The Hepatic Circulation

By

CHARLES G. CHILD, III, M.D.

PROFESSOR OF SURGERY, TUFTS COLLEGE MEDICAL SCHOOL,
CHAIRMAN, DEPARTMENT OF SURGERY,
NEW ENGLAND CENTER HOSPITAL;
FORMERLY ASSOCIATE PROFESSOR OF CLINICAL SURGERY,
CORNELL UNIVERSITY MEDICAL COLLEGE,
ATTENDING SURGEON, NEW YORK HOSPITAL

ILLUSTRATED

W. B. SAUNDERS COMPANY

and

Portal Hypertension

From the Department of Surgery and the
Laboratory of Surgical Research
of the New York Hospital–Cornell Medical Center

IN COLLABORATION WITH

WARD D O'SULLIVAN, M D

MARY ANN PAYNE, M D

GEORGE R HOLSWADE, M.D

ROGER MILNES, M D.

HELENA GILDER, M D

ARTHUR L GORE, M.D

CHARLES S HARRISON, M D

DANIEL M HAYS, M D

DAVID BARR, M D.

ROY D MCCLURE, JR., M D

EARL A O'NEILL, M D

PHILADELPHIA AND LONDON · 1954

Made in United States of America

Press of W. B Saunders Company Philadelphia

Library of Congress Catalog Card Number 54-5324

TO MY WIFE

MARGARET

PREFACE

As originally conceived, this book was to have been limited to a consideration of the normal and pathological anatomy and physiology of the portal venous system It was my intent to discuss the clinical aspects of this unique venous circulation and to review the many related experimental studies which have been made upon it, not only in laboratory animals but in man as well In this fashion, it was hoped to bring together in one volume a useful body of information concerning this poorly understood blood vascular system

Early in the development of the manuscript, I realized that one of the three circulations of the liver could not be separated logically from the other two Consequently the scope of this volume was broadened to consider not only the portal venous system, but also the intimate circulatory dynamics of blood flowing to and from the liver In accepting the responsibilities of this more ambitious effort, I have drawn freely upon the investigations of others It is my sincerest hope that those who find their names in this volume will not take offense The subject of the liver and its related vascular structures, I have discovered, constitutes a large research and clinical field sorely taxing the abilities of any one essayist To those, therefore, who have kindly permitted me to reflect their views and to reproduce certain of their illustrations I am most particularly indebted

It is my hope that, as published, this volume will enable the basic scientist to appreciate some of the clinical problems which confront the physician and surgeon in their efforts to manage successfully patients with hepatic disease and related disorders Conversely, I believe that clinical scientists may benefit from a broader understanding of the fundamental problems involved in any disease process Briefly stated, the major objective in writing this book is to help close the gap in time which always seems to exist between discoveries of the basic sciences and their clinical application to disease

Insofar as the original studies contained in this volume are concerned, I must pay tribute to the resident system by which young surgeons are trained Since its introduction into this country over a half century ago by Dr William Stewart Halsted, this system of surgical training has always maintained as one of its major tenets a

period of time devoted to laboratory investigation. Only by early association with the disciplines of research may an awareness be aroused of the important relationship existing between the surgical experimental laboratory and progress in clinical surgery To the several resident surgeons, past, present and future, who have contributed to this volume I must express my gratitude and appreciation Without their help, their many inspirations, and their tireless efforts, this book would never have been written In this day of faltering and indecision with regard to residency training programs in surgery, I would urge that the ideals of Dr Halsted be kept more strongly in mind than ever before

To my teacher and recent chief, Dr Frank Glenn, I would express especial thanks, not only for his encouragement and help in the preparation of this volume, but also for the privilege of working in the laboratories of surgical research at Cornell Medical College and upon the surgical wards of the New York Hospital To the memory of my professors, Dr George J Heuer and Dr. William DeWitt Andrus, I would pay important tribute, for they were surgeons, skilled in their art, convinced of the place of research in surgery, and loyal beyond measure to the ideals of resident training in surgery For the friendship of Dr N C Foot and Miss Margaret Boise I am and ever shall be grateful

I should be remiss indeed were I not to express my appreciation to Miss Louise Cross for her work upon the text and its bibliography; to my secretary, Miss Nan Wilkinson, for her cheerful and discerning efforts in behalf of the manuscript and its many revisions, to the W B Saunders Company, for their generous support and resourcefulness in publishing this volume, and to the National Institutes of Health for their many grants-in-aid without which this volume would have been impossible

CHARLES G CHILD, III, M.D

CONTENTS

Chapter 11

Chapter 12

Chapter 13

Chapter 14

Chapter 15

Chapter 16

APPENDICES

Appendix 1

Appendix 2

CHAPTER 1

Introduction

FROM time to time in the development of the art and science of surgery, new therapies are devised and old ones undergo important revisions. Currently, the relationship between diseases of the liver and its several circulatory systems is the subject of surgical interest and attack. Portal hypertension, although its existence had been suspected for many years, has recently been accurately defined. It has also assumed a position of clinical importance, for today significant elevations in portal pressure can be reduced to harmless levels.

Abdominal ascites due to cirrhosis of the liver has long been regarded as secondary to splanchnic congestion. Numerous unsuccessful efforts have been made surgically to relieve patients of this troublesome manifestation of hepatic disease. During recent decades, however, biochemical studies have indicated that large amounts of fluid collecting within the abdominal cavity may more properly be related to metabolic deficiencies or abnormalities. Consequently, direct surgical attacks upon ascites fell for a time into disfavor and were discarded one by one. Within the past few years, however, interest in the surgical treatment of ascites has been revived through a more comprehensive understanding of intrahepatic circulatory relationships. Intractable collections of abdominal fluid have apparently responded to hepatic arterial ligation.

Although from time to time a few surgeons have suspected that man could survive sudden occlusions of his portal vein, it has been proved only within the past few years that this large vein could be resected were it found invaded by a malignant tumor. Another one [illegible]

a host of heretofore undreamed of experimental techniques have been developed to further knowledge concerning this complex organ. How many of these may prove to be important clinically cannot yet be estimated.

In spite, however, of these many advances in the physiology of

epatic circulation and in spite of many improvements in the medi-
al and surgical treatment of hepatic diseases and their various
nanifestations, much yet remains to be learned The many factors
oncerned in hepatic regeneration have yet to be clarified. What role
he lymphatics of the liver play in the normal economy of the organ
nd how these are adversely affected by disease is poorly understood
oday The physiology of the hepatic artery in health and disease is
s yet far from clear Why can this vessel and its branches be suc-
essfully resected in some animals and not in others? Why is hepatic
rterial ligation fatal in men whose livers are normal, yet apparently
ompatible with life when the liver is the site of cirrhosis? That ele-
ated levels of portal pressure can be lowered by shunts fashioned
etween the portal and systemic circulations is today a matter of
ecord Yet the operations required are long, difficult, and hazardous
uch major efforts have these proved to be that surgeons over the
orld have sought to devise some less formidable and yet equally
ffective operation Furthermore, as far as can be determined, mere
eduction of portal pressure does not improve liver function in any
ay Those who advocate hepatic arterial ligation, however, do ap-
ear justified in claiming that at least they are making some effort
ward improving the status of the liver itself

mber of laboratory and clinical investiga-
ting intrahepatic cir-
ulatory dynamics ... erning the inter-
elationships of the portal vein, the hepatic ... he hepatic artery,
nd the intrahepatic lymphatics remain unsolved In addition to the
rge number of details which must still be learned about the liver
nd its blood and lymph vessels, there exists today much confusion
nd little clarity concerning the large body of facts and observations
n this subject which have accumulated over the years What new
nformation will be forthcoming in the future is a matter of con-
ecture, the problem at hand concerns what is known today of the
ormal liver, its complicated vascular systems, and the various dis-
ases in which its vessels are implicated

As the large number of essays upon the blood vessels of this organ
e reviewed, numerous contradictions of seemingly basic facts can
e found The observations of one author cannot be correlated with
ose of another Experiments reproducible in one laboratory are
und not to check with those in another To what, then, can all
ese apparent discrepancies be attributed? In all probability, they
an best be ascribed to the innumerable methods of investigation
hich have been employed Not only have investigative techniques
aried, but, in addition, the livers of any number of different animals
ave been studied and efforts made to reduce these to a common

denominator When drugs, hormones, and toxic substances have been used in the course of an investigation, their dosages and methods of administration have been found to be widely divergent When dyes, particulate matter, or colloids have been injected into one or more of the hepatic vessels, particle size and injection pressures have varied extensively. In some studies, injections have been made during life, while in others specimens have been prepared for study after death In this great diversity of investigative effort, then, can probably be found a valid explanation of the many discrepancies in information on hepatic hemodynamics which exist today

These problems and others, the significance of which is probably quite unsuspected today, have provided the stimulus for the preparation of this monograph If it successfully portrays some of the important aspects of hepatic physiology as this is understood today and serves to interest a few in the many problems which remain unsolved, it will have accomplished its purpose

CHAPTER 2

Historical Background

ALMOST from the beginnings of recorded time, the liver has been the object of much speculation, study, and experimentation. By the ancients it was accorded a position of first importance in bodily function. They thought that in the liver the blood mixed with the chyle and from there spread out through the entire body. In addition, they accorded the liver a prominent position in many religious rites, particularly those concerned with animal sacrifice and soothsaying. Galen regarded the liver as the focus of animal heat and as an organ intended for the formation of blood and for the origin of the veins. By his pretense to omniscience, Galen successfully held up any advance in true knowledge of the liver until the sixteenth century. Audacious indeed was Vesalius when at the age of twenty-nine he described the course of the veins, the various relationships of the liver, and the true anatomy of the heart. Not only did Vesalius change the entire course of medical thought by exposing the errors in Galen's speculations, but he also paved the way for clarification of the hepatic circulation. Accurate knowledge, however, of the portal and hepatic veins and the hepatic artery had to await the epoch-making discovery of the circulation of the blood by Harvey in 1628. This, together with the perfecting of the microscope, really marks the origin of modern appreciation of hepatic anatomy and physiology.

In 1640, fourteen years before Glisson's classical description of the hepatic capsule appeared, Waleus pointed out that there were as many branches of the hepatic artery as there were branches of the portal vein or bile ducts and that these structures all lay in close proximity encased in a common sheath. Glisson in 1654 elaborated the vascular nature of the stroma of the liver, and suggested that its primary usefulness was for the support of its weight. Glisson also clearly demonstrated by an experiment that portal blood passed through the liver and into the vena cava. At a dissection in London, he filled a large ox bladder with water and a little milk. This reservoir was fitted with a pipe which in turn was tied into the portal

vein near the liver. On squeezing the bladder, the milky water passed through the liver, entered the vena cava, and thence entered the right sinus of the heart. As more of the milk-tinged water was passed through the liver, the organ lost its red color and became pale. This observation led Glisson to conclude that portal blood bathed not only the large hepatic vessels, but the capillaries as well. Glisson also noticed that numerous small arteries penetrated the substance of the liver. In conjecturing at some length as to their function, his curiosity was perhaps the first to be aroused on the various functions performed by the portal vein and hepatic artery. Why, he asked, did an organ so richly supplied with portal blood actually need an arterial circulation?

Wepfer in 1664 and Bidloo in 1685 both recognized that the liver was composed of multiple small bodies. In 1685 Malpighi also established the fact that the human liver, as well as that of shellfish,

in function and he termed them acini.

In 1694 William Salmon translated Diemerbroeck's popular book, "The Anatomy of Human Bodies," into English, and for the first time gave the English-speaking peoples a complete picture of the anatomy of the liver. That the era of speculation was fast giving way to the new medical science of observation and experimentation is reflected in Diemerbroeck's comments on the old and the new. He wrote in 1672: "Concerning the Office of the Liver there are various Opinions, of which the Ancientist and the most revered is from Galen who saith that Sanguinification is compleated in the Liver, and that it is the true and primary sanguifying or blood making bowel. But this Opinion, after the discovery of the Circulation of the Blood has been wholly abolished, since it is found that the Blood is only made in the Heart. . . . Malpighi, who has examined the substance and inner parts of the liver most accurately by his microscope, . . . has observed many things unheard of, and hitherto altogether undiscovered. . . . But Malpighi, by reason of these new Golden Inventions seems unwilling to call the liver a Bowel for the future, but

cation and there has been worshipped for many Ages by the common consent of Physic, yet that in these our times it should be torn and

depos'd from its throne and despoil'd of all its Sovereignty, nay that it should be said to be dead " It was not, of course, the liver which was dead but Galen

During the next 150 years, only a few significant observations were recorded In 1749 Ferrein showed that the hepatic artery supplies the portal space and its associated structures and then is drained by way of the radicular portal vein into the lobule itself In 1781 Sabatier expressed the view that Glisson's capsule was a prolongation of the tissue surrounding the mesenteric veins Thereby was formed a structure by which blood from the digestive tract was aided in reaching the liver This view was later, in 1802, supported by Laennec Lieberkuhn apparently recognized during this early period that injection techniques provided a tool for determining accurately the vascular arrangements of the liver Muller, crediting Lieberkuhn with the first experiments of this type, pointed out in 1830 that all of the vessels in the liver seemed to communicate with each other

To Francis Kiernan (1833) must go the credit for the first complete description of the hepatic vessels. He described Glisson's capsule as a cellulovascular membrane in which the portal vein and hepatic artery divide and subdivide into their smallest branches After the vessels reach their smallest subdivisions, the capsule then forms a sheath about each lobule He demonstrated conclusively that the hepatic artery supplies the bile ducts and the walls of the portal veins as well as the loose areolar tissue in which these structures lie Kiernan supported Ferrein thus far, but here the views of these two early investigators diverged Ferrein believed that the hepatic arterial blood entered the lobule directly, while Kiernan felt equally sure that it was collected and entered the portal vein. Kiernan also showed that neither the hepatic arterial branches nor those of the portal vein could be injected by way of the hepatic veins. He did not believe that the lobules received anything but the smallest amount of arterial blood directly Thiele (1844), Weber (1850), and Beale (1856) added little of importance to Kiernan's original descriptions In 1865 MacGillavry first noticed a space lying between the liver cell and its blood vessels This was later (1890) described by Dissé and given his name The significance of this narrow space was unknown For a long time it was thought to be an artefact, but recently it has come again into prominence and today it is believed to represent the intralobular lymphatic system

Hyrtl (1864) studied the hepatic arterial circulation in amphibians and reptiles and concluded that the hepatic artery empties directly into the portal vein capillaries In this fashion the hepatic lobule receives a mixture of arterial and portal venous blood In 1863 Betz believed that he had demonstrated that fluids injected into the

portal vein and hepatic artery were mutually exclusive. Of particular interest are the careful studies of Chrzonszczewsky which were published in 1866. Employing dye inject on techniques and selective ligation of the portal vein, hepatic artery or hepatic veins, this author concluded that every lobule of the liver could be divided into two territories, central and peripheral. The central was fed principally but not wholly by the hepatic artery, the peripheral was entirely nourished by the portal vein.

From approximately 1870 to 1920, these issues concerning the distribution of the hepatic vessels were widely studied and discussed. Although Kiernan and his school had succeeded well in establishing the hepatic lobule as a vascular unit, there were some who were impressed with the glandular nature of the organ and sought to make the liver primarily a biliary gland. Kiernan maintained that the central vein constituted the axis about which the lobular unit of the liver is formed. Brissaud and Sabourin in 1884, however, opposed this view, maintaining that the bile duct system should be considered the central unit. This biliary concept although popular for a time, was finally discarded largely because it began to be recognized that the liver possessed many functions other than the excretion of bile. Bichat, in his famous "Anatomie Generale," postulated that nature would not have made the organ so large were its only function that of producing a secretion less abundant than urine. Within a few years, Claude Bernard established the liver as an organ of major endocrine importance and the vascular concept of the hepatic unit has persisted ever since.

Another problem which dominated hepatic physiology during this period concerned how the high pressure in the hepatic artery and the low pressure in the portal vein were equalized. Gad in 1873 concluded from his experimental work that the hepatic artery brought oxygenated blood to the liver and also mechanically controlled portal flow. He believed that the hepatic arterial branches joined those of the portal vein at an acute angle. In this fashion, a flap-like valve was formed which not only effectively reduced arterial pressure but also controlled the flow of blood through the portal vessels. Although not specifically stated, Kiernan's explanation for the equalization of portal venous and hepatic arterial pressure apparently lay in the fact that the arterial blood had to pass through a capillary bed before entering the portal vessels.

Additional studies upon hepatic arterial blood flow have been made from time to time: in 1922 by Pfuhl, in 1927 by Loeffler, in 1930 by Cameron and Mayes, and in 1930 by Olds and Stafford. These investigators in general confirmed Kiernan's original observations, while the latter two expressed the belief that branches of the

hepatic artery passed directly to the hepatic sinusoid. Cameron and Mayes believed these vessels constituted only a small part of the sinusoidal circulation Olds and Stafford, on the other hand, maintained that small arterioles entering the sinusoids constituted the main mode of distribution of the hepatic artery.

For the most part, the studies recorded in the immediately preceding paragraphs can conveniently be called anatomical They largely concerned conclusions drawn from the examination of microscopic slides of the liver prepared either with or without the benefit of injection of dyes or particulate matter of one sort or another. Many investigators expressed varying degrees of dissatisfaction with these techniques, pointing out, as did Chrzonszczewsky as early as 1866, that variations in rate of administration, in dosage, in injection pressure, in species of animal, and so on, might well account for the many differences of opinion which were expressed as well as for the numerous disagreements concerning the precise arrangement of the hepatic vasculature For these reasons, a few men as early as 1900 and many recent investigators turned to what may be termed the physiological approach Although these more dynamic studies contributed new information, they also added their share of confusion

Perhaps the first man to concern himself seriously with the dynamics of the portal circulation was Herrick In 1907 he perfused normal human livers and found a large volume of blood in the portal vein circulating at a low pressure In the hepatic artery, the reverse was true—a small volume of blood flowed at high pressure He also found that alteration in arterial pressure had little effect upon portal pressure Here, then, were studies directed primarily toward determining if possible how the blood moved about through the liver Like others, Herrick became interested in how the pressures in these two systems equalized themselves before the blood drained out through the hepatic venous system He postulated only two possibilities—the entering circulations influenced each other either by direct communication or by lateral pressure In effect, then, Herrick incorporated both views of the earlier anatomists those of Kiernan postulating a capillary bed interposed between the hepatic artery and the sinusoid, and those of Gad proposing a flap valve mechanism

During the next few years, thinking about the hepatic circulation was dominated by the studies of Burton-Opitz, who became interested in the relative amounts of blood passing through the liver by way of the portal vein and the hepatic artery His original figures of 75 per cent coming from the portal vein and 25 per cent from the hepatic artery were in general confirmed by other investigators (Barcroft and Shore, McLeod and Pearce) Grab, Janssen, and Rein (1929), however, estimated that perhaps not over one-sixth of the

blood supplied to the liver is from the hepatic artery In 1932 McMichael undertook a study of the hepatic circulation as reflected in its vasomotor reactions He made careful studies upon the reaction of the portal pressure to epinephrine, acetylcholine, and vasopressin and demonstrated that a definite control is exerted over hepatic blood flow by neurogenic and hormonal mechanisms More recently still, Knisely, Mann, and many others have developed techniques for observing lobular blood flow directly By this method, the actual responses of the hepatic blood vessels to drugs, hormones, dyes, particulate matter, and nervous stimulation can be critically examined. This technique has successfully resolved many, but by no means all, of the divergent opinions of anatomists, pathologists, and physiologists

Thus the study of the circulation of the liver has progressed over three hundred years from gross observation through microscopic examination of fixed (and oftentimes injected) tissue to actual observation of the dynamics of blood flow under both normal and abnormal conditions Mann, in his address in 1942 to the students at Indiana University, stated that the story of the circulation of the liver is buried under its own literature Few truer words were ever spoken What can be accepted today as verifiable fact and reasonable conjecture on the circulatory components of the liver?

CHAPTER 3

Comparative Anatomy of the Hepatic Circulation

IN the evolution of animal species, the liver cannot be found until a digestive system has made its appearance In its most primitive form, the intestinal tract consists simply of a cavity with a single opening serving both as mouth and anus As such a structure, the gut first makes its appearance in the coelenterates, that phylum to which belong coral, jelly fish, and sea anemones Here the liver is represented merely by a cellular thickening in the dorsal wall of the digestive cavity (Fig 1) With the appearance of animals with a muscular digestive tube which includes both mouth and anus (worms, molluscoids, and balanoglossus), a pair of glandular diverticula can be identified just caudal to the pharynx These are believed to function as a liver (Fig 2) Although the better developed of these primitive forms of animal life have a closed circulatory system with dorsal and longitudinal vessels and even a contractile area in the aorta, the liver is without any recognizable vascular connections At this stage in its evolution, the liver is clearly glandular This fact undoubtedly served as the stimulus for a number of early anatomists to orient the structure of the liver in terms of its glandular rather than its vascular pattern

A liver manifesting both glandular and vascular components is first seen in the Amphioxus, a small fish-like animal with a cartilaginous rod running the entire length of its back This animal, conveniently manifesting features interpreted as characteristic of a transition from invertebrate to vertebrate, possesses a diverticulum located just below the pharynx and projecting from the digestive tube As the vascular system in this animal is traced, blood is found propelled through the gills, collected in a dorsal aorta, and passed down to the tail The blood returns through the postcardinal and the subintestinal vein The latter vessel breaks up into capillary ramifications within the liver from which blood is recollected in a short hepatic vein which enters the sinus venosus into which the

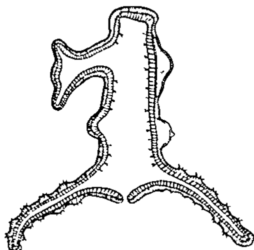


Fig 1. Hydra Certain of the cells lining the enteric cavity of this primitive organism are presumed to function as the liver of higher forms of animal life As far as is known, the secretory function of these specialized cells is entirely external. (Modified from Neal and Rand Comparative Anatomy The Blakiston Co)



Fig 2 In many primitive forms of animal life, the liver can be recognized ... e function ... lified from ... k Co and



CHAPTER 3

Comparative Anatomy of the Hepatic Circulation

IN the evolution of animal species, the liver cannot be found until a digestive system has made its appearance In its most primitive form, the intestinal tract consists simply of a cavity with a single opening serving both as mouth and anus As such a structure, the gut first makes its appearance in the coelenterates, that phylum to which belong coral, jelly fish, and sea anemones Here the liver is represented merely by a cellular thickening in the dorsal wall of the digestive cavity (Fig 1) With the appearance of animals with a muscular digestive tube which includes both mouth and anus (worms, molluscoids, and balanoglossus), a pair of glandular [illegible] can be identified just caudal to the pharynx These are [illegible] liver (Fig 2) Although the better devel- [illegible] closed circulatory system with dorsal [illegible] even a contractile area in the aorta, the liver is without any [illegible]zable vascular connections At this stage in its evolution, the liver is clearly glandular This fact undoubtedly served as the stimulus for a number of early anatomists to orient the structure of the liver in terms of its glandular rather than its vascular pattern

A liver manifesting both glandular and vascular components is first seen in the Amphioxus, a small fish-like animal with a cartilaginous rod running the entire length of its back This animal, conveniently manifesting features interpreted as characteristic of a transition from invertebrate to vertebrate, possesses a diverticulum located just below the pharynx and projecting from the digestive tube As the vascular system in this animal is traced, blood is found propelled through the gills, collected in a dorsal aorta, and passed down to the tail The blood returns through the postcardinal and the subintestinal vein The latter vessel breaks up into capillary ramifications within the liver from which blood is recollected in a short hepatic vein which enters the sinus venosus into which the

In a number of primitive and in most advanced fishes (elasmobranchs, including sharks, rays, and chimaeras), there can be found many general features which must be considered developmental refinements. For instance, in some the stomach is J shaped, a pylorus is present, a duodenum can be recognized, and the pancreas is well developed. In many species, the liver becomes a multilobed structure of considerable size, a configuration which this organ retains throughout even the most advanced forms of animal life. The spleen is now well established as a part of the portal system. The heart is further developed, but the sinus venosus remains unabsorbed. From the dorsal aorta just below the branches leading to the aortic arches, a long celiac artery proceeds some distance before sending branches to the liver, stomach, and intestines. The portal system collects blood from the gastrointestinal tract through the following veins: the gastric, the duodenal, the pancreatic, the ventral intestinal, the anterior gastrosplenic, and the posterior intestinal. All these join the main portal stem slightly above the pylorus and proceed in a long main trunk to the liver (Fig. 4). In addition, certain other venous changes occur in the direction of the mammalian system. The caudal vein divides, forming two branches which break up to traverse the mesonephron whence the blood is carried by the new subcardinals, thus forming the renal portal system. Lateral abdominal veins also enter the common cardinals.

In the lungfish, with partial air breathing, pure and impure blood is separated to some extent in the first step toward full lung breathing instead of gill breathing. A branch of the hepatic vein extends upward along the pulmonary fold to play a part in the formation of the new post-cava which originates in a connection between the posterior cardinals in the region of the kidney. The blood from the posterior part of the body henceforward increasingly follows this route to the heart, and the old arches of the post-cardinals shrink until in more advanced animal forms they become the azygos veins. In the study of more advanced forms of animal life, minor differences are encountered, but radical departures from the now firmly established basic portal pattern cannot be found. In the urodele, the lateral abdominal veins fuse to form a single ventral abdominal which enters the portal vein rather than the duct of Cuvier as it does in the shark. This unique connection between the systemic and portal circulation is well demonstrated in the frog (Fig. 5).

In the bird, the vascular pattern is in general reptilian, but a number of interesting changes in hepatic circulation appear. The celiac artery is well developed and supplies the liver with arterial blood by way of a distinct hepatic artery. The superior mesenteric artery, however, arises as a trunk separate from the celiac. The ventral abdominal

common cardinals also empty. Thus, the Amphioxus manifests the first portal system (Fig. 3). It is quite correct, then, to state that the portal system appears in the first vertebrate and, as will be seen shortly, becomes a characteristic of all vertebrates.

LOWER VERTEBRATES

In most primitive vertebrates such as the cyclostomes, the liver makes one further differentiation over the pattern seen in the Amphioxus. It is *no longer a diverticulum but becomes a closed organ* with a well developed ductile system. Interestingly enough, the gallbladder is present in the larval stage of the cyclostomes, but it dis-

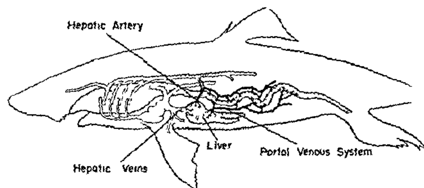


Fig. 4. Squalus. In this primitive fish all elements of the hepatic circulation are fully developed. Arterial blood is carried through a hepatic artery; portal venous blood travels to the liver through a well developed portal venous system, hepatic blood is returned to the heart through the hepatic veins. Furthermore, the liver is completely developed, sinusoids are present, and there exists both internal and external secretory function. (*Modified from* Neal and Rand. *Comparative Anatomy*. The Blakiston Co.)

appears by the time adult life is reached. Furthermore, *in them the* liver is known to produce enzymes active in digestion. The subintestinal and supraintestinal veins participate in the formation of a portal system which collects blood from the intestinal tract and, as in the Amphioxus, passes it through the liver. By this time, there is a three-chambered heart, and a definite hepatic artery can be identified.

In lampreys and hagfishes, comprising as they do one of the lowest forms of vertebrates, the liver manifests its final evolutionary development. It is an organ of both internal and external secretion. There is an arterial blood supply, a portal system, an hepatic venous system, and well developed sinusoids. Its ductal drainage system for transport of its external secretion is complete (Fig. 4).

to have undergone a number of changes. These vary from species to species as well as within species. The variations from species to species are important in the study of the hepatic circulation, and failure to recognize these has undoubtedly accounted for many of the confusing reports concerning the normal physiology of the hepatic circulation. For instance, the cat and dog die promptly

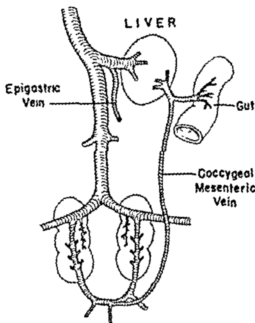


Fig. 6. Bird. In this vertebrate a unique connection between the systemic and portal venous system exists in the form of a vein connecting the postcaval with the portal vein via the inferior mesenteric vein. Ligation of the postcaval vein in effect produces in the bird a reverse Eck fistula. Higgins, Mann and Priestley took advantage of this unique circumstance in their studies of hepatic regeneration after partial hepatectomy. (Redrawn from Adams: Comparative Anatomy—An Introduction to Vertebrates. John Wiley & Sons.)

after sudden occlusion of the portal vein whereas, under similar circumstances, the monkey and man survive. Variations within species, of course, constitute anomalies and are considered in detail in a later section.

In the mammal, the sinus venosus is finally absorbed into the heart, and the aorta leaves that organ by a single arch on the left. The renal portal system has completely disappeared, and the lateral abdominals are represented only as the fetal vitelline veins. The

vein, figuring prominently in certain reptiles, is replaced by the coccygeal mesenteric vein which enters the portal vein as do the ventral abdominals The epigastric vein, however, enters the hepatic vein above the liver This is one of the few examples of the entry of a systemic vein, or any vein for that matter, into the hepatic drain-

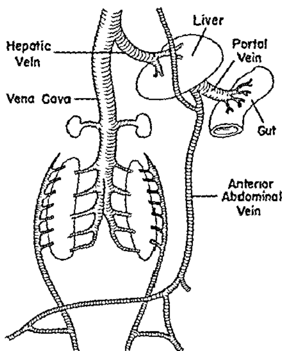


Fig 5 Frog Here, too, the portal venous system is fully developed but presents an additional feature—a large systemic vein, the anterior abdominal vein, drains into the portal system *In observing reactions of the liver to substances injected directly into it, this anterior abdominal vein has proved exceptionally useful* Through it particulate matter, dyes, drugs and other substances may be injected into the liver without entering the peritoneal cavity (Redrawn from Adams Comparative Anatomy—An Introduction to Vertebrates John Wiley & Sons)

age system As will be seen later, these peculiar arrangements in the bird have contributed significantly to the study of hepatic regeneration (see Fig 6)

MAMMALS

Along with other developmental advances in the cardiovascular system, the liver and its associated structures in mammals are found

to have undergone a number of changes. These vary from species to species as well as within species. The variations from species to species are important in the study of the hepatic circulation, and failure to recognize these has undoubtedly accounted for many of the confusing reports concerning the normal physiology of the hepatic circulation. For instance, the cat and dog die promptly

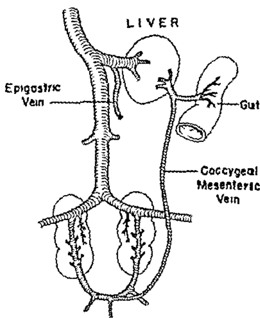


Fig. 6. *Bird*. In this vertebrate a unique connection between the systemic and portal venous system exists in the form of a vein connecting the postcaval with the portal vein via the inferior mesenteric vein. Ligation of the postcaval vein in effect produces in the bird a reverse Eck fistula. Higgins, Mann and Priestley took advantage of this unique circumstance in their studies of hepatic regeneration after partial hepatectomy. (Redrawn from Adams: Comparative Anatomy—An Introduction to Vertebrates. John Wiley & Sons.)

after sudden occlusion of the portal vein whereas, under similar circumstances, the monkey and man survive. Variations within species, of course, constitute anomalies and are considered in detail in a later section.

In the mammal, the sinus venosus is finally absorbed into the heart, and the aorta leaves that organ by a single arch on the left. The renal portal system has completely disappeared, and the lateral abdominals are represented only as the fetal vitelline veins. The

may remain in anastomoses, the coccygeal mesenteric vein has dropped its caudal connections and has become the superior mesenteric vein contributing to the portal system (Fig. 7). The intestine

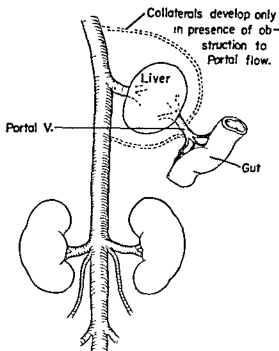


Fig 7 Mammal Here the portal system is completely separated from the systemic venous circulation Only when abnormal obstruction to portal blood flow develops do important portal systemic collaterals appear (Modified from Adams Comparative Anatomy—An Introduction to Vertebrates John Wiley & Sons)

of mammals is greatly elongated, and in them for the first time the *cloaca is replaced by separation of the rectum from the urogenital* organs. Duodenum, jejunum, and ileum are clearly defined, and there is full differentiation between colon and rectum.

of the right lateral is a clearly separated caudate lobe. There is also some variation in lobulation from species to species, and from indi

vidual to individual In the primates, the liver is exceedingly large and pushes the stomach to a lower plane than in man The primate liver is trilobed with right and left lobes placed dorsally and a single ventral lobe The right and central lobes are intimately connected, but the left lobe remains quite free and may even have a separate ligament attaching it to the diaphragm The lobulation of the gorilla, however, resembles more the earlier lobulated form found in the rat, rabbit, cat, and dog

The arterial and venous supply to the liver is naturally affected by the degree of hepatic lobulation, separation of the liver into several lobes requires more points of entry for these vessels than when it is compact The common duct varies accordingly In the dog, the portal vein receives two main branches, the first bringing blood from the stomach and pancreas, the second from two mesenteric branches which are joined by the gastroduodenal and pancreatic vessels In the cat, the effects of extensive lobulation are well illustrated by the entry of the portal vein into the different lobes by five separate branches of the main trunk Butler, studying the foregut plexus of the albino rat which is derived embryologically from the splanchnic somatic mesoderm, points out that this plexus gives rise to pulmonary veins and to veins of the trachea, esophagus, and stomach, and that the veins which drain the caudal third of the esophagus connect with the portal system He finds intimate connections both in arterial and venous systems between gut and lung and mediastinum A direct connection between the portal and pulmonary veins by way of the perivagal veins normally remains in the adult rat and guinea pig In man, this remains only as venae comitantes of the vagus, joining the left gastric to the bronchial veins with small connections with the extrapulmonary portions of the pulmonary veins The degree to which pulmonary, portal, and systemic veins remain attached varies from lower animals to man, but connections are always present and may be enlarged under certain circumstances

In higher animals such as the monkey and man, there is an important anatomical feature which, though it does not concern the portal circulation specifically, profoundly affects certain of its dynamics This feature apparently relates to the retroperitoneal position of portions of the pancreas, the duodenum, the spleen, and the right colon In such common laboratory animals as the rat, cat, and dog, the pancreas, spleen, and right colon are in what might be designated an intramesenteric position In studying the anatomical relationships in these animals, it is evident that collateral venous channels which drain these organs into the systemic venous circulation are scant In the monkey and man, however, these organs occupy

... structures emptying into the post-cava. In mam-
... from
the caudal region ... ces
... anastomoses, the coccygeal ... has
... mesen-
... tine

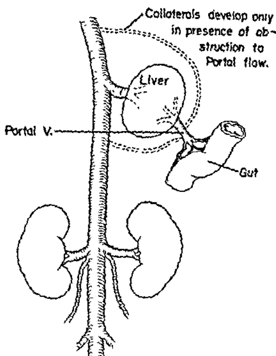


Fig 7 Mammal Here the portal system is completely separated from the systemic venous circulation Only when abnormal obstruction to portal blood flow develops do important portal systemic collaterals appear (Modified from Adams Comparative Anatomy—An Introduction to Vertebrates. John Wiley & Sons)

and man also are more apt to present a broader mesenteric base than can be found in the cat or dog These anatomical peculiarities, possibly associated with assuming the upright position, account for the fact that the monkey and man can survive sudden and complete occlusion of the portal vein whereas the cat and dog immediately succumb to this operation (Fig 8)

a more retroperitoneal position Particularly is this true of the pancreas and duodenum This retroperitoneal position, of course, places these organs in greater apposition to the body wall than is the case, for instance, in the cat or dog Although not as striking as in the pancreas and duodenum, the spleen and right colon of the monkey

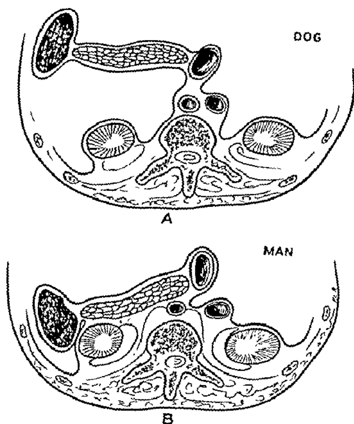


Fig 8 Relative position of the pancreas and portal vein of the dog and man with respect to the retroperitoneal tissues A. Dog In this animal the pancreas and portal vein lie between the leaves of a well developed mesentery Here little opportunity is provided for natural portacaval anastomoses. B Man In man as well as in other primates the pancreas and portal vein lie in a retroperitoneal position Here ample opportunity is provided for the development or persistence of numerous portasystemic venous connections It is this circulatory difference which permits man to survive sudden portal venous occlusion while the dog dies Natural portasystemic shunts provide adequate portal decompression in man Since no such shunts occur naturally in the dog, this animal bleeds to death into his splanchnic capillary bed following sudden portal occlusion

and man also are more apt to present a broader mesenteric base than can be found in the cat or dog These anatomical peculiarities, possibly associated with assuming the upright position, account for the fact that the monkey and man can survive sudden and complete occlusion of the portal vein whereas the cat and dog immediately succumb to this operation (Fig 8)

CHAPTER 4

Embryology of the Liver and Its Blood Vessels

GROSS EMBRYOLOGY

EVEN a *cursory survey of the history of embryology reveals that* for many hundreds of years anatomists and physicians have consistently manifested interest in the early development of man and of lower animals In these studies, the fetal circulation received extensive attention Not only were the general circulatory dynamics of the developing embryo accorded detailed investigation at an early date, but the vessels of the liver proved a particularly attractive subject This was undoubtedly due to the fact that in the embryo the *umbilical vein, leading as it does directly to the liver, is such a prominent* vessel that it could hardly fail to raise questions concerning its functional relationships Galen in the second century A D. fitted this large vein into his general concepts of the hepatic veins; it was just another vein finding origin in the liver The views of Galen held sway until the sixteenth century when Vesalius and Fabricius of Aquapendente independently described the ductus venosus Fabricius' illustrations in "De Formato Foetu" of the venous relationships of the liver during fetal life have hardly been improved upon and are reproduced in Figure 9 These show that the complex anatomical relationships of the umbilical vein, the portal vein, and the ductus venosus were clearly understood at this time

When Harvey began his studies of the circulation, enough was known of the fetal vascular peculiarities to focus his attention upon this aspect of the blood vascular system In his treatise published in 1628, Harvey wrote, "In the embryo the liver has practically no function—the umbilical vein passes intact through that viscus, and from the porta hepatis there is an opening so that blood returning from the intestines makes for the heart, not through the liver but by the aforesaid umbilical vein " From Harvey's time on through the 1800's, the anatomical era flourished, and many carefully executed studies of the intrahepatic venous circulation were published. In 1736, Trew described the extrahepatic and intrahepatic circulation,

and examination of his diagram reveals that he had an excellent grasp of the essential relationships (Fig. 10).

Von Haller (1757) perhaps drew the first physiological deductions from anatomical facts when he wrote that the greater part of fetal

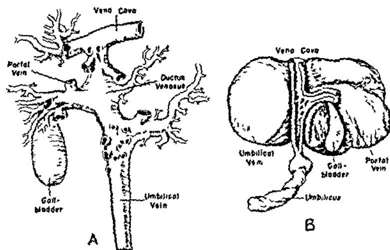
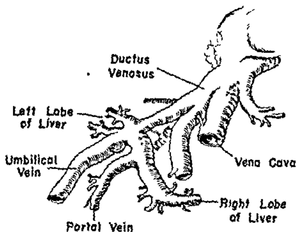


Fig. 9 About 1577 Fabricius of Aquapendente studied the fetal circulation *It is obvious from these two illustrations that Fabricius was well informed on* gross anatomy of the umbilical, portal, and hepatic venous blood flow



was concerned.

blood passes from the iliac into the umbilical arteries (and thence to the placenta). The blood returning (from the placenta) passes to the umbilical vein, one seventh going directly to the vena cava, while six sevenths pass through the liver By wax injections of the human fetal liver, Bertin demonstrated that the left lobe of the liver is supplied mainly from the umbilical vein, while the right lobe

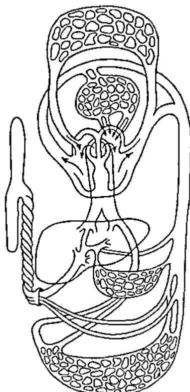


Fig 11 Reproduction of Ziegenspeck's original diagram of the fetal circulation For the first time the complete story of circulatory dynamics was understood (Redrawn from Ziegenspeck Samml klin Vortrage, Gynak no 148, 1905)

receives blood from branches common to both the umbilical and portal veins Bichat reported in 1801 that certain of his studies indicated the presence of a spur of tissue at the beginning of the ductus venosus which he believed partially prevented portal blood from entering the ductus He also noticed that the liver was relatively larger during fetal life than in the adult. The anatomical era came to a close with Ziegenspeck's complete description of the fetal circulation which he published in 1910 His diagrammatic representation

of the fetal circulation is reproduced in Figure 11 The solution of gross physiological problems in fetal circulation came somewhat later in the twentieth century with the studies of Pohlman, Kellogg, Barcroft, and Barclay Blood gas analyses and roentgen visualization of intrahepatic and extrahepatic blood flow in living specimens have all but completely clarified fetal cardiovascular physiology

MICROSCOPIC EMBRYOLOGY

While but a few investigators seem to have been interested in gross development of the hepatic vascular system, many have concerned themselves with the microscopic anatomy of the developing liver and its blood vessels The foundation for modern microscopic embryology is "The Anatomy of Human Embryos," published in

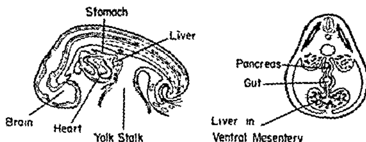


Fig 12 Transverse and sagittal section of a pig embryo at the end of the fourth week The hepatic diverticulum is clearly evident at this stage (From Patten Human Embryology The Blakiston Co)

1880 by Wilhelm His In this monograph, the early development of the liver is completely elaborated In this country, Mall, interested specifically in the liver, published in 1906 a summary of his many studies of this organ This treatise included not only the embryological development of the liver, but also the minute anatomy of this organ in its adult form In recent years, Patten, one of the country's foremost embryologists, has interested himself in this field Because of the completeness of His's, Mall's, and Patten's studies, a detailed description of the development of the liver in this volume is unnecessary A brief résumé, however, may be helpful in understanding better certain aspects of the liver's complex vascular arrangements

The primordial outgrowth of cells destined to become the liver appears in the endodermal lining of the foregut during the fourth week of life This grows with remarkable rapidity and pushes out between the two layers of splanchnic mesoderm which at this time represents the ventral mesentery of the gut (Fig 12) Almost as soon as the hepatic cells begin their expansion, they invade the omphalo-

mesenteric veins, breaking these up into small capillaries later known as sinusoids. At twenty-two days, the hepatic diverticulum commences its rapid growth and invades the adjacent splanchnic mesenchyma This is reflected over the surface of the growing glandular mass of the liver and ultimately gives rise to the connective tissue capsule of the liver as well as to the interstitial connective tissue of



... ver The hepatic ... human embryo ... m Textbook of Histology)

the liver lobules Except for the capsule and the scant fibrous tissue supporting the lobules, there is surprisingly little connective tissue formed about the developing hepatic cells. Instead of connective

grow around segments of the omphalomesenteric vessels or whether the hepatic cellular aggregates grow into these vessels and thereby become invested with endothelium is not known In an embryo of 16 mm , liver cells appear in direct contact with sinusoidal endothelium The accompanying figure, redrawn from Maximow and Bloom, demonstrates this relationship (Fig 13)

As growth progresses, a characteristic pattern is established The liver plates continue to grow, each carrying with it an investment of

endothelium to form the myriads of sinusoids evident in the adult liver. The confluence of many sinusoids constitutes at one end the afferent portal venules and at the other the central veins of the efferent hepatic venous system. This intimate application of sinusoidal endothelium to the hepatic cell is important in light of the active discussion waged today over whether a "space," presumably lymphatic, exists between the endothelium and the liver cell. Maximow, in his detailed study of the liver, was unable to demonstrate a definite relationship of the lymphatics to the liver cell, or of lymphatic capillaries to the liver lobule. Only in the periportal connective tissue about the ramifications of the portal vein can lymphatic vessels be identified (Fig. 14).

Because the mammalian embryo has practically no food supply in the form of yolk, it is dependent for survival upon the precocious establishment of blood circulatory relationships within its mother. Very early in its development, therefore, masses of mesoderm aggregate and promptly hollow out into tubes. Within a relatively short time, these assume the pattern of adult arteries and veins, the former leading from the heart and supplying blood to all embryonic structures, while the latter drain blood back toward the heart. In the capillary bed of the intestinal tract and yolk sac, conventional arteriovenous relationships appear early and ultimately differentiate into an arterial supply system and venous drainage system. In approaching the hepatic circulation, a somewhat different situation obtains. The developing hepatic plates invade the omphalomesenteric vessels to form the afferent and efferent venous circulatory system of the liver. Precisely when the arterial system gains access to the hepatic sinusoids has not been clearly defined. That arterioles arising from branches of the celiac axis enter the sinusoid in adult life has been demonstrated many times, but when and how this occurs is not known. Although veins arise in the same manner as do arteries, they become clearly defined somewhat later. For this reason it can be assumed that the mesenchymal space, later to be invaded by the developing hepatic primordium, is well supplied by arterial components by the time the omphalomesenteric veins become differentiated.

For arteriovenous anastomoses to form normally at this time would be distinctly unusual, for it is rare that arterioles enter a large venous lake except upon a basis of congenital defect. Whether the developing liver cells, as they push into and trabeculate the omphalomesenteric veins, are able to force some form of unusual arteriovenous connection between the hepatic arterioles and the developing sinusoids is only a matter of conjecture. That a developing organ such as the gut or the liver carries with it its own arterial supply is

mesenteric veins, breaking these up into small capillaries later known as sinusoids. At twenty-two days, the hepatic diverticulum commences its rapid growth and invades the adjacent splanchnic mesenchyma This is reflected over the surface of the growing glandular mass of the liver and ultimately gives rise to the connective tissue capsule of the liver as well as to the interstitial connective tissue of



The hepatic
man embryo
Textbook of
Histology)

the liver lobules Except for the capsule and the scant fibrous tissue supporting the lobules, there is surprisingly little connective tissue formed about the developing hepatic cells. Instead of connective tissue, endothelium predominates As a thin membrane, this invests the developing parenchyma and forms an enormously complex maze of capillaries constituting the sinusoids Whether the liver tubules ... vessels or whether
vessels and thereby
In an embryo of
h sinusoidal endothelium. The accompanying figure, redrawn from Maximow and

established The
an investment of



Fig 14 Reproduction of Lee's superb illustrations of the intrahepatic lymphatics These surround both hepatic venous systems and in areas actually occupy an intramural position Although these can be traced along the finest venules, connections with the sinusoids have never been demonstrated (From Lee Contributions to Embryology, vol 15, 1923)

umbilical veins of a seven weeks human embryo are shown in Figure 16

As the umbilical blood flow shifts from the sinus venosus to the liver, it tunnels a channel more or less directly through liver substance This intrahepatic portion of the umbilical vein becomes known as the ductus venosus Although recognized many years ago as one of the distinguishing features of fetal circulation, its exact physiological significance has never been satisfactorily explained

vestigators, by employing serial roentgenograms and contrast media

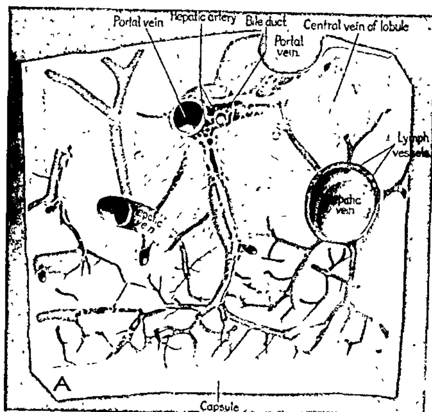


Fig. 14. See opposite page for legend

well known, and it may be argued that though the omphalomesenteric veins are primarily large vessels carrying blood from the gut, they must have small branches draining the mesenchymatous tissue in which the liver will ultimately develop. Thus, as the liver enlarges, it not only fragments the omphalomesenteric channels, but also carries with it the original capillary bed of the septum transversum In this fashion, arteriovenous communications at the capillary level could readily appear during the course of development of the sinusoid This may be the explanation for the direct entrance of the arterioles into the sinusoids

Two of the most interesting rearrangements of the fetal blood flow occur at about the fifth week, the right omphalomesenteric vein is obliterated leaving the left to serve as the ultimate portal vein, and the main flow from the umbilical vein shifts from its extrahe-

was seen entering the liver about 1 cm from the ventral hepatic border. Shortly after entering the liver, it gave off numerous small branches delivering blood to the left side of this organ. The greater proportion of blood flowing through the ductus passes directly on through the liver, entering the inferior vena cava by way of the hepatic veins. By injecting a mesenteric vessel with contrast media, Barclay was also able to show that portal blood supplied the right

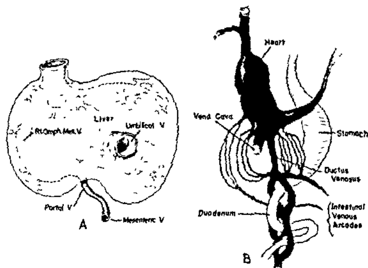


Fig. 16. A. Reproduction of one of Mall's timeless illustrations demonstrating beautifully the relationships in intra-uterine life of the huge umbilical vein, the small portal vein, and the hepatic venous drainage system. (... embryo 6.5 mm long.) (From Mall, Am. J. ...
B. Gilfillan's ...
vein. The la... to do so, in ... for the congenital defects encountered ... at birth or in adult life.

side of the liver. These relationships as well as the general proportions of blood reaching each side of the liver are shown in Figure 17. Although Barclay clearly points out that in his injection studies the contrast medium passing through the duct... that passing through ... tion of the ... what part ... roentgenog... cava directly, while ...

The d...

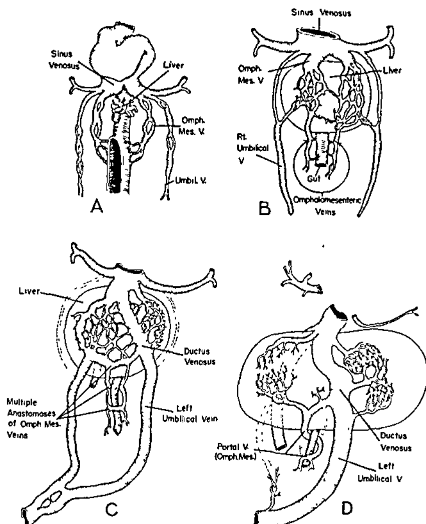


Fig 15 Patten's reconstruction of the developing portal venous system In A (four weeks) is shown the hepatic diverticulum surrounded by the omphalomesenteric venules In B (five weeks) the expanding liver had al-

sphincter can be recognized is seen in Figure 18. The stimulus to closure of the sphincter is not definitely known. As it appears to be under control of the vagus, it may close by neurogenic stimuli initiated at birth. On the other hand, it may be a simple mechanical process initiated by sudden lowering of umbilical vein pressure. In man, the relationships of these structures are essentially those found in sheep. Such variations as exist seem to be of minor importance. In Figure 19 is reproduced one of Barclay's illustrations showing this sphincter in man. As soon as umbilical blood flow ceases, the liver shrinks markedly in size, and portal blood flow through the portal



Fig. 19. Microscopic section of the umbilical venous sphincter in man. This lies at the junction of the umbilical vein (U.V.) with the ductus venosus (D.V.). (From Barclay, Franklin, and Prichard. The Foetal Circulation. Blackwell Scientific Publications.)

sinus is accelerated. The liver is now wholly supplied with venous blood by way of the portal vein.

During fetal life the hepatic artery is small, and on several occasions Barclay points out that when injected, the flow of the contrast medium through it is negligible compared with the amounts of blood pouring into the liver by way of the portal and umbilical veins.

Returning now to the embryology of the liver, it will be recalled that this subject was somewhat unceremoniously dropped in favor of the ductus venosus at a time when the embryo had reached a length of 4 to 5 mm. (fifth to sixth week). From this point on, development is rapid, and the several branches of the extrahepatic portal system become well defined. By the eighth week, the main hepatic vein is well developed, and the vena cava can readily be identified. The vascular pattern of the liver is, as Mall has shown, complete in all its adult respects by 24 mm. (eighth week). In Figure 20 is reproduced one of Mall's superb illustrations demonstrating the state of development at 24 mm.

As the hepatic portal venous system is developing from the umbilical and omphalomesenteric systems, the umbilical vein lies in

ing oxygenated blood directly to the heart. One of the most interesting aspects of this structure is its "sphincter" mechanism which is located at its origin and which closes at birth. Thus, severe hemor-

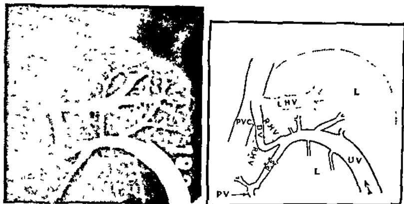


Fig. 17. In their classic roentgenographic studies of the fetal hepatic circulation Barclay and his associates demonstrated all the essential features of these complex circulatory systems. The roentgenogram reproduced above together with its identifying diagram is self-explanatory. (From Barclay, Franklin, and Prichard. The Foetal Circulation. Blackwell Scientific Publications.)

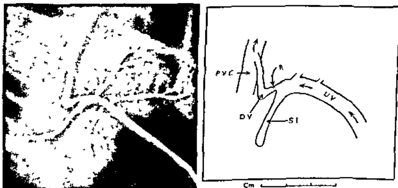


Fig. 18. Another of Barclay's superb roentgenograms of the hepatic circulation in the fetus (sheep just prior to term). Of particular interest is the notched segment R of the ductus venosus. This Barclay has demonstrated

rhage from the umbilical cord at birth is prevented. Barclay, studying his roentgenograms of this structure shortly before birth, was able to demonstrate that the sphincter became increasingly unstable and underwent rhythmic contractions. The notching by which the

the well recognized collaterals occurring in cirrhosis of the liver
d
a
E
portasystemic communications Their early observations as well as

Suffice it at this point to emphasize that all of the pathways for the development of portal collaterals are laid down during embryological life

Of importance embryologically is the stellate cell of Kupffer which forms part of the lining of the sinusoid or actually constitutes the entire lining of these structures These large cells are recognized

[illegible]

therefore, to establish the Kupffer cell as part of the reticuloendothelial system

It will be seen that the life history of the pathways of hepatic blood flow is indeed a varied one The earliest parenchymal cells are presumably nourished by hepatic arterial but non-oxygenated blood and are drained by branches of the omphalomesenteric vein These then acquire a complex internal capillary system known as the sinusoids During this phase, the liver cells grow rapidly on blood derived from the arterial system and from the developing gut Ap-

venosus At the beginnings of this structure, a sphincter has been demonstrated which seems primarily designed to prevent back-bleeding after division of the umbilical cord at birth It is so placed that,

such close proximity to the subcardinal veins that interconnections develop between the portal and systemic circulations. Thus, there is an embryological pattern in primates and man for the persistence of both large and small connections between the portal vein and vena cava Large portavenous communications have been described, but they are rare The more usual form of anastomoses between these two venous circulations are small vessels They appear because of the close proximity between the visceral and systemic vascular plexus in early embryological development. As the gut develops and becomes fixed to the posterior parietal wall, ample opportunity is

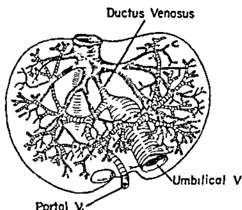


Fig 20 Relative degrees of development of the portal vein, the umbilical vein, and the ductus venosus in a 24 mm. pig embryo (Redrawn from Mall. Am J Anat, vol. 5, 1906)

afforded for innumerable fine portasystemic venous communications to form The greater number of these occur, of course, in the pancreaticoduodenal bed, the root of the small and large bowel mesentery, and in relationship with the renal-sexual organs For these reasons, certain animals, principally the primates, survive sudden interruption of portal blood flow, while occlusion of the superior mesenteric vein leads to gangrene of the bowel. In man, adequate provision has apparently been made for secondary drainage of the gut, whereas arterial supply is without functionally effective collaterals Madden, by injection techniques, has been able to demonstrate pre-formed portacaval venous shunts of some magnitude in 50 per cent of his specimens

Little did Ruysch realize the controversy which he was starting when in 1738 he demonstrated that wax injected into the vena cava filled portions of the mesenteric veins. Over the intervening years, an active discussion has waged as to the precise pathways by which

CHAPTER 5

Anomalies of the Hepatic Vasculature

MANY years ago, Pliny wrote that "Nature creates monsters for the purpose of astonishing us and amusing herself" Twins, monsters, and congenital anomalies together with other aspects of teratology have been recognized in one form or another from the beginning of medical history To account for these slips of nature, many theories have been evolved, many relevant and a few irrelevant statistics collected, and a vast amount of experimental work performed Yet even today all too little precise information is available concerning their etiology Apparently, there are many factors concerned, any one of which can, under proper circumstances, produce anatomical defects

Stockard, in his famous experiments upon the common minnow, showed that all deleterious trends seemed to manifest one factor in common, namely, the ability to slow or to stop growth Stockard believed that this process could be highly selective in that growth inhibition could be limited to one organ or to one minute part of an organ Furthermore, it could be self-limiting in the sense that the inhibiting effect might operate for only a short period of time Although Stockard's concepts of "developmental arrest" have served to explain satisfactorily many puzzling aspects of anomalous development, they have been found to leave much to be desired For instance, there are many anomalies which, as Patten has so ably emphasized, seem "due to such widely divergent processes as growth which has gone too far, resorption which has gone too far, resorption which has not gone far enough, or growth fairly normal in amount but in an abnormal location" A single or blanket explanation obviously seems inadequate Until a more satisfactory knowledge of anomalies is acquired, it would appear sounder to temper the wholesale use of "developmental arrest" with some less specific and more general term such as developmental defect

Mackay has expressed the opinion that there can be no doubt but that many congenital malformations are determined genetically and that they are hereditary At the same time, he emphasizes the fact that many may be caused wholly by a variety of environmental in-

were it to function during fetal life, a greater share of umbilical blood could be diverted from time to time through the hepatic sinusoids Under these circumstances, the mechanics of portal flow are such that were the sphincter of the ductus to close, a greater proportion of fetal portal blood would simultaneously traverse the liver Whether or not any such intrahepatic alteration of umbilical and portal blood flow occurs during intra-uterine life is as yet unknown Immediately after birth, the major portion of total hepatic afferent blood flow shifts from the highly oxygenated umbilical to the poorly oxygenated portal, and circumstances as they exist in adult life are initiated. The most striking feature, of course, is the sudden marked decrease in total flow as well as the sharp decrease in total oxygen supply Apparently, the liver cell is able to withstand these many changes in its environment quite uneventfully. That the ductus venosus is essential may, of course, be questioned, for in some mammals it is entirely absent

It may be noted that in all
this discussion of the embryology
of the liver nothing has been
said about the Biliary duct
which on the basis of its glandular
structure should form the stem
, branches around which the
acini of the liver lobules should
form

that Kiernan in 1833 again examined it in the museum of St Bartholomew's Hospital and confirmed the original description He also concluded, as had others, that bile could be formed from hepatic arterial blood alone In 1804 Wilson described a similar case, that of a girl thirteen who died of a head injury Here again, the portal vein entered the inferior vena cava There were two splenic veins,

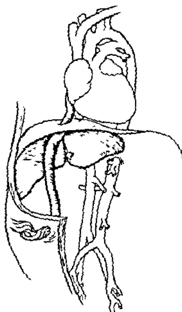


Fig 21 Unusual anomaly of the umbilical vein described by Shryock Here the umbilical vein grooved the anterior surface of the liver, pierced the diaphragm, and entered the right auricle This infant also presented numerous other anomalies (From Shryock Anat Rec, vol 82, 1942)

one entering the portal vein and one the vena cava In both of these instances, the liver was entirely normal The hepatic artery appeared about twice its usual size These, then, are two well authenticated cases of the portal vein entering the vena cava, its blood reaching the heart without traversing the liver The embryological explanation undoubtedly lies in the fact that at about the fifth week, the omphalomesenteric vein lies sufficiently close to the developing subcardinals (these ultimately form the vena cava) to permit the formation of a permanent anastomosis with the systemic system rather than with the liver As emphasized by Edwards, the embryological explanation for the entrance of the portal system into the vena cava probably lies

fluences such as maternal diets deficient in one or another vitamin. Recently, Gregg has shown conclusively that rubella in the mother is an etiological factor in congenital cataract and heart disease provided the disease occurs during the first three months of pregnancy Fraser and his associates have added yet another factor by demonstrating experimentally that congenital defects in the offspring can be induced by injecting cortisone into pregnant mice.

At the present time, it seems unlikely that a single factor will ever be proved to be the cause of all congenital anomalies; it appears more than probable that ultimately they will be shown to be due to a series of factors, some hereditary and many environmental

In focusing attention upon the anomalies of the circulatory cir- [illegible]

the liver, it was shown that this organ develops amid a welter of important blood vessels. These lie in such close proximity that almost infinite opportunity is offered for variation before the final pattern is reached Furthermore, as these vessels develop in pairs, anomalies [illegible]

quate venous supply and drainage for the liver It can hardly be said that in themselves hepaticoportal anomalies are important clinically in the sense that they present syndromes either incompatible with life or requiring surgical correction A few surgical cases, however, have been reported in which anomalies have made operative cure of one disease or another difficult if not hazardous or even fatal. The surgeon must, therefore, ever be aware of variations upon the normal hepatic blood flow when he is called upon to deal surgically with diseases of the upper mid-abdomen To review all of the anomalies of the hepatic circulatory system which have been recorded would carry this volume far beyond plausible dimensions Only a limited summary, therefore, of the major anomalies of this circulatory system which seem of special interest or surgical importance will be outlined here

THE PORTAL VEIN

Perhaps the first adequately documented anomaly of the hepatic venous system is that of Mr Abernethy reported in the "Philosophical Transactions for 1793." In this patient, a child, the portal vein terminated in the inferior vena cava Of such interest was this specimen in relationship to the physiological problem of whether bile was secreted from the hepatic arterial or portal venous blood

denum degenerated instead of the left Since the left lies directly in front of the duodenum, the portal vein persisted in this position throughout the remainder of development and on into adult life Should a patient with this anomaly develop cancer of the pancreas, pancreaticoduodenectomy would doubtless be greatly facilitated

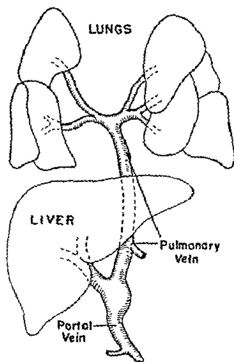


Fig 23 Anomaly of the portal vein Perhaps this might more properly be considered an anomaly of the pulmonary vein Certainly both vessels, however, are concerned in this distinctly unusual drainage of the pulmonary vein into the portal vein (Redrawn from Young Arch Path, vol 44, 1947)

Fraser and Brown have also reported a congenital anomaly of the portal vein which is of some interest A small portal vein was found in its normal position, but in immediate association with it were a large number of small, thin-walled veins This, these authors believed, simply represented persistence to adult life of many of the small vessels which go to form the portal

Another anomaly of surgical importance is one described by Young and by Weinberg and Kolson Here the pulmonary veins entered the portal vein This unusual venous arrangement is diagrammatic-

in the persistence of the supracaudal system. This may be associated in its suprarenal component with reception of the portal and right pulmonary vein by the vena cava

Another anomaly of the hepatic system concerns the umbilical vein In the case described by Shryock and his associates, the single umbilical vein simply grooved the liver but did not enter it. It then pierced the diaphragm to enter the right auricle (Fig. 21). The portal vein and liver were normally developed. In explaining this deformity,

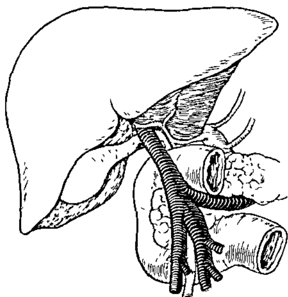


Fig 22 Anomaly of the portal vein In this unusual case, the portal vein and all its tributaries lay anterior to the head of the pancreas and duodenum (Redrawn from Knight Ann Surg, vol 74, 1921.)

the authors expressed the belief that it resulted from an incomplete invasion of the [illegible]

vein, therefore, [illegible]

up one interest [illegible]

is apparently not dependent for normal development upon the torrents of oxygenated blood poured through it by the umbilical vein during fetal life

An anomaly of the portal vein which might prove of considerable surgical hazard were it not recognized is one in which the portal vein and its major tributaries lie ventral to the head of the pancreas and duodenum This abnormality has been described by Knight and is diagrammed in Figure 22 In explanation, Knight points out that here the right limb of the venous loop which surrounds the duo-

lomesenteric vessels should persist, a simple explanation for this anomaly is forthcoming Another possible explanation for this rare anomaly is found in Butler's description of the development of the pulmonary venous plexus This arises from that part of the foregut [illegible] course, readily explain the entrance of the pulmonary veins into the portal Another anomaly appears when the umbilical vein fails to be obliterated at birth. This has been described by Karabin in a young girl of twenty-four years who presented herself for the treatment of a large cyst in the ligamentum teres which was successfully removed at operation

Although the exact explanation for the appearance of congenital strictures in hollow organs is not known, they constitute a well recognized group of abnormalities in both the arterial and venous systems In the portal system, only a few references to congenital stricture can be found Therefore, the report by Mahoney and Hogg is particularly important Here in two infants, these authors found a tight stricture of the portal vein at the porta hepatis (Fig 24) Both of these patients presented the picture of extrahepatic portal obstruction with severe portal hypertension In view of the fact that portasplenic communications are common, it is difficult to explain why these did not develop sufficiently during intra-uterine life to provide adequate portal decompression Particularly is this perplexing when it is realized that the obstruction in these children must have been present for a long time, even before birth As Mahoney points out, both of his patients were strikingly lacking in collaterals about the hilus of the liver Apparently, they both were deficient in their share of normally occurring shunts

THE HEPATIC ARTERY

Because of their importance in operations upon the extrahepatic biliary tract, anomalous sites of origin and pathways of the hepatic artery have been extensively studied One of the most complete reports on this subject is that of Browne which is based upon 280 dissections of the cadaver In his analysis, Browne found two basic abnormalities, the first concerned the origin of the artery, the second concerned its course In slightly over 90 per cent, the common hepatic artery originated from the celiac axis As such, the common hepatic artery was absent in 5 per cent, the liver being supplied with arterial blood from a variety of neighboring sources. In four dissections, the common hepatic arose from the superior mesenteric, while in two it arose as a single vessel from the aorta

ally portrayed in Figure 23 Although there is no little confusion as to precisely how the pulmonary veins develop, there is one stage at which the umbilical vein, the omphalomesenterics, the splanchnic, and the cardinals all converge Most of the communicating channels disappear, but if one between the developing pulmonary and ompha-

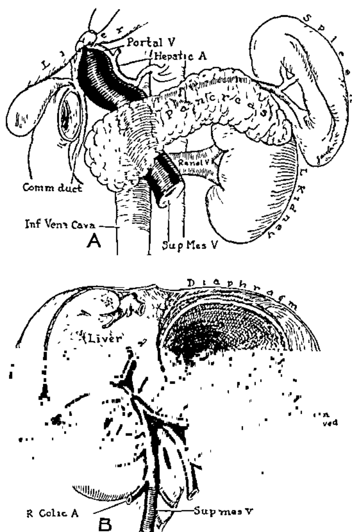


Fig 24 Anomaly of the portal vein Practically all tubular structures are subject to stricture formation and the portal vein is no exception. In these ... of portal hypertension was encountered which ... is anastomosis (From Ma

lomesenteric vessels should persist, a simple explanation for this anomaly is forthcoming Another possible explanation for this rare anomaly is found in Butler's description of the development of the pulmonary venous plexus This arises from that part of the foregut venous plexus which surrounds the lung bed It, therefore, originally drains into the portal venous system Although later it obtains a new and final route, persistence of the original pattern would, of course, readily explain the entrance of the pulmonary veins into the portal Another anomaly appears when the umbilical vein fails to be obliterated at birth This has been described by Karabin in a young girl of twenty-four years who presented herself for the treatment of a large cyst in the ligamentum teres which was successfully removed at operation

Although the exact explanation for the appearance of congenital strictures in hollow organs is not known, they constitute a well recognized group of abnormalities in both the arterial and venous systems In the portal system, only a few references to congenital stricture can be found Therefore, the report by Mahoney and Hogg is particularly important Here in two infants, these authors found a tight stricture of the portal vein at the porta hepatis (Fig. 24) Both of these patients presented the picture of extrahepatic portal obstruction with severe portal hypertension In view of the fact that portasplenic communications are common, it is difficult to explain why these did not develop sufficiently during intra-uterine life to provide adequate portal decompression Particularly is this perplexing when it is realized that the obstruction in these children must have been present for a long time, even before birth As Mahoney points out, both of his patients were strikingly lacking in collaterals about the hilus of the liver Apparently, they both were deficient in their share of normally occurring shunts

THE HEPATIC ARTERY

Because of their importance in operations upon the extrahepatic biliary tract, anomalous sites of origin and pathways of the hepatic artery have been extensively studied One of the most complete reports on this subject is that of Browne which is based upon 280 dissections of the cadaver In his analysis, Browne found two basic abnormalities; the first concerned the origin of the artery, the second concerned its course In slightly over 90 per cent, the common

sections, the common hepatic arose from the superior mesenteric, while in two it arose as a single vessel from the aorta

Singh and Sohal have recently added another type of congenitally abnormal origin of the hepatic artery. In their case, it arose from the left gastric artery. Out of Browne's 280 dissections, there were 10 instances of distinctly abnormal course; in 8 the artery passed far enough to the patient's right to lie in front of the common bile duct (Fig 25 A and B); one passed posterior to the portal vein (Fig. 25 C); and one passed behind the common duct (Fig 25 D).

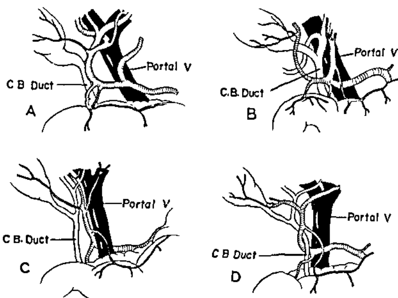


Fig 25 Representative examples of the more common anomalies of the hepatic artery It is remarkable how constant is the portal vein and how inconstant the hepatic artery (From Browne Surgery, vol 8, 1940)

In studying the right and left hepatic arteries, Browne found considerably greater variation than existed in the common. In 80 per cent, the right originated normally, that is, from the common hepatic, but pursued an abnormal course Two passed behind the portal vein, 6 swung anterior to the common bile duct, and 55 passed anterior to the common hepatic duct In 44 of these, the right hepatic artery traveled in such close proximity to the neck of the gallbladder that it would easily have constituted a serious hazard in cholecystectomy.

In the remaining 20 per cent, various abnormalities in origin of the hepatic artery were found, 8 arose from the aorta and 9 from the superior mesenteric artery When an abnormal origin was encountered, a high percentage of these vessels passed posterior to the portal vein In a rather appreciable number of instances, a true

accessory right hepatic artery could be identified, and in one instance there were two accessory right hepatic arteries

In dissecting out the left hepatic artery, Browne found that only 65 per cent arose normally from the common hepatic artery In the remaining instances, the vessel arose either separately from the

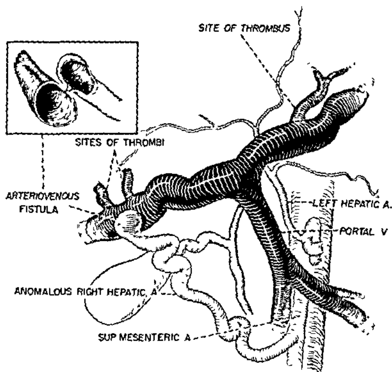


Fig 26 Anomalous hepatic artery and arteriovenous fistula between this and the right branch of the portal vein (From Strickler, Lufkin, and Rice Surgery, vol 31, 1952)

celiac axis, or from the aorta, or from the superior mesenteric artery Occasionally, accessory arteries existed Another exhaustive study of the hepatic artery and its branches is that of Michels appearing in 1951 In general, the findings of this anatomist substantiated earlier reports

Congenital anomalies of the hepatic circulation cannot be finally dealt with without some consideration of arteriovenous communications outside the liver That they exist within the liver is well established In discussing a paper on the surgical physiology of the

portal venous system read by Child before the New York Surgical Society in February 1952, Blakemore expressed the opinion that an anomaly such as an arteriovenous fistula between the arterial and portal system might account for cases of portal hypertension in which neither cirrhosis nor an extrahepatic portal block could be demonstrated. In a recently studied case of portal hypertension, a

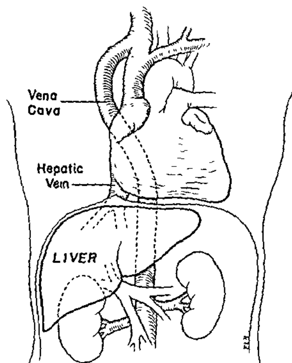


Fig. 27. In this unusual anomaly the hepatic vein enters the right auricle instead of the vena cava (after Effler).

portal block could not be demonstrated, and there was no evidence of cirrhosis of the liver. Yet the pressure in both the portal and splenic veins was 32 cm. of saline. This set of circumstances might be interpreted as indicating an arteriovenous fistula. Recently, Strickler and his associates reported a patient in whom an arteriovenous fistula existed between an anomalous right hepatic artery and the right branch of the portal vein. These authors were inclined to explain this abnormality upon the basis of a congenital aneurysm of the hepatic artery which eroded into the portal vein rather than upon the basis of a congenital fistula (Fig. 26).

THE HEPATIC VEINS

In turning to the hepatic veins, the only anomaly which is commonly found does not primarily affect this vessel but rather the vena cava On occasion, the vena cava may develop distinct from the [illegible]

hepatic vein enters the auricle directly (Fig 27) In the human case, failure to recognize this caval anomaly during an intrathoracic operation for cancer led to the death of the patient, for this vessel was inadvertently ligated under the impression that it was a large azygos vein. The patient died in shock

CHAPTER 6

The Gross and Microscopic Anatomy of the Intrahepatic Vasculature

GROSS ANATOMY OF THE HEPATIC VESSELS

TEXTBOOKS on anatomy generally give a complete description of the extrahepatic portal venous system and its several components However, the impression is gained that knowledge of the intrahepatic blood vessels is incomplete and fragmentary. Actually, this is far from the truth As early as 1654, Glisson studied the distribution within the liver of the hepatic artery and the portal and hepatic veins So accurate is his original plate that it is reproduced in Figure 28

In later years, Rex (1888), Mall (1906), Evans (1912), Segall (1923), and Hjortsjo (1948) thoroughly studied the numerous branches of the portal vein, the hepatic veins, and the hepatic artery. The descriptions by all of these authors correspond very closely and yield the impression that there is little more to be learned about the gross anatomy of these vascular structures The most recent investigators in this field are Elias and Petty (1952), who carefully reviewed all previously reported studies in the light of their own original investigations The following brief description of the main intrahepatic blood vessels has been taken largely from the studies of these two authors

Immediately upon entering the liver the main portal vein divides ... ly stated ... the left ... concept, however, has been shown to be incorrect It can be demonstrated that these main trunks supply areas of hepatic tissue which do not conform to the various lobes of the liver As a result of his studies on the intrahepatic distribution of the portal veins, Hjortsjo was ... two He designated these ... ut that in the adult the ... (Fig 29)

The development of these territories is presumed to be in response to the changes in venous blood flow which take place within the liver during its development For instance, in fetal life the left hepatic territory is larger
delivers to it a greater am
territory through the omp



Fig 28 It is obvious from this original study of Glisson that as long ago as 1654 the gross anatomy of the intrahepatic vessels was well understood (Redrawn from Glisson's original plate in Elias and Petty Am J Anat, vol 90, 1952)

ately after birth, these size relationships reverse themselves because after closure of the umbilical vein, the greatest amount of blood reaching the liver is through the portal vein In this connection, there is another influence which also effects a greater increase in size of the right over the left side This is found in the fact that the right main trunk leaves the main portal trunk at a less acute angle than does the left This produces a streamlined effect, in itself capable of delivering a greater amount of blood to the right side than to the left After birth, this favorable circulatory pattern on the right enables the right side of the liver far to outgrow the left At about three years of age, the dividing plane between the right

and the left territories corresponds to that seen in the adult (Fig. 30).

From each of the two main portal trunks arise innumerable branches supplying blood to the hepatic parenchyma After passing through the sinusoids, the hepatic blood is collected for return to

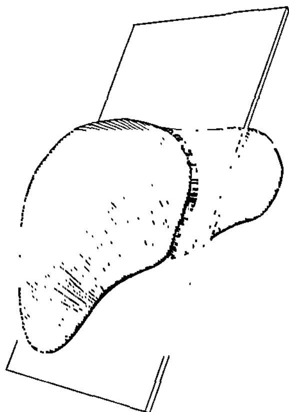


Fig. 29 Hjortsjo's plane Although it is commonly held that the liver is divided into right and left lobes with respect to the major portal venous branches, Hjortsjo has shown that this is not so Rather is the hepatic mass divided obliquely and unequally into two territories (Redrawn from Hjortsjo· Acta Anat, vol 11, 1951)

the general circulation by way of the hepatic venous system The hepatic venules interdigitate with those of the portal system and form progressively larger veins which ultimately drain into the vena cava Actual entrance into the vena cava is by way of three major and several smaller vessels In general, the hepatic venous system is much simpler in its arrangement than is the portal. Figure 31, re-

drawn from Elias and Petty, shows nicely the gross anatomical relationships of the hepatic and portal venous systems in the adult

Of further gross anatomical interest in Elias and Petty's studies is the fact that when either one or the other of the intrahepatic venous systems (portal or hepatic) is injected alone, the resulting

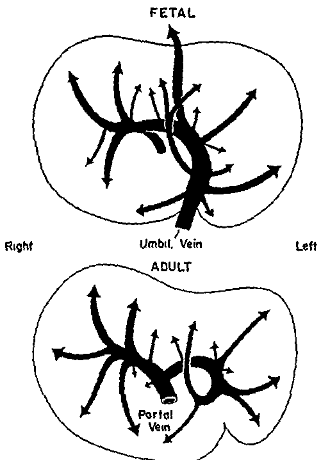


Fig 30 Comparison in sizes of the hepatic lobes during fetal and adult life In the upper drawing is diagrammatically portrayed the relatively greater size

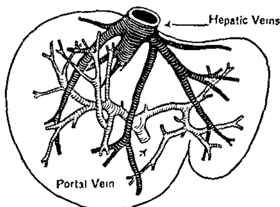


Fig 31. Elias' concept of the important gross anatomical branches of the portal and hepatic venous trees in the adult. (Redrawn from Elias and Petty: Am J Anat, vol 90, 1952)

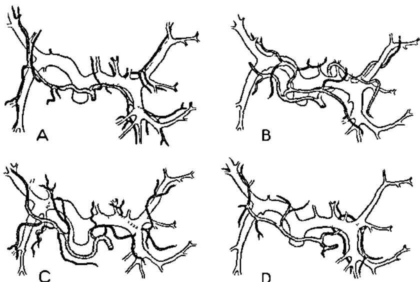


Fig 32 Even as the extrahepatic segments of the hepatic artery are inconstant, so are the intrahepatic branches of this vessel The above inconsistencies are reproduced from Elias' studies of this subject. (From Elias and Petty Am J Anat, vol 90, 1952)

cast can be teased apart into its smallest components. Where these are injected simultaneously, an homogeneous mass results which cannot be separated This demonstrates the complete interdigitation

to the two venous systems in which consistency is the rule. In Figure 32 is diagrammatically portrayed the extreme inconsistency of the hepatic arterial distribution within the liver

MICROSCOPIC ANATOMY OF THE HEPATIC VESSELS

The liver, as a composite glandular organ with both incretory

basic anatomical as well as the functional unit of the liver has for many years been termed the lobule Architecturally, this has been regarded as composed of hepatic cells with a cord-like tubular or trabecular arrangement This time-honored concept has recently been challenged by Elias and his associates who have demonstrated to their

laminae per

The walls b

one hepatic

separated into its individual components, it has been found profitable to do so for clarity in description

The Hepatic Lobule

The mosaic of small polygonal areas which were first (1664) observed by Wepfer in the pig undoubtedly first gave rise to the concept of the liver lobule which has persisted to this day As techniques for microscopic examination of tissues became available,

liver lobule be considered as centering about the smallest element of the biliary ductile system. Although this glandular concept of the hepatic unit enjoyed some measure of popularity for a time,

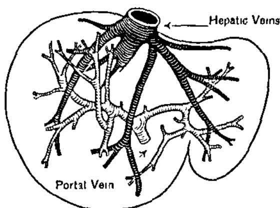
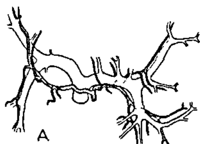
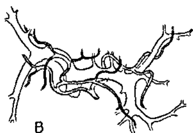
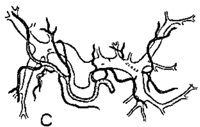
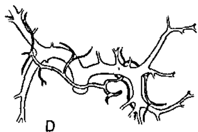


Fig 31 Elias' concept of the important gross anatomical branches of the portal and hepatic venous trees in the adult (Redrawn from Elias and Petty Am J. Anat, vol 90, 1952)









[illegible]

Petty Am J Anat, vol. 90, 1952)

which contain the sinusoids In mammals, the parenchymatous walls separating neighboring sinusoids are one cell thick

As a starting point for the development of this concept of hepatic structure, Elias requests his students to eliminate all intrahepatic

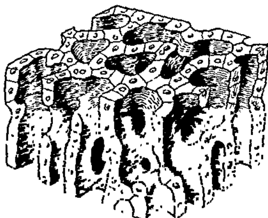


Fig 33 No more appropriate legend for Elias' diagrammatic representation of the basic cellular structure of the liver is to be had than his own words " . the spaces in which the sinusoids are suspended are separated from one another by walls of hepatic cells These walls are one cell thick (and) form a continuous system of anastomosing plates, much like the walls separating the rooms within a building These rooms, the 'lacunae hepatis' are, however, much taller than wide. Many doors and windows connect them, the walls separating them are crooked, as are the rooms themselves Thus the vast system of these spaces constitutes a labyrinth which pervades, without interruption, entire liver lobes " (Reproduced from Elias Am J Anat, vol 85, 1949)

structures except the liver cell, conceiving of all structures lying in between the cells simply as space Beginning at a hypothetical central space (in reality the smallest distinct branches of the hepatic vein), Elias describes plates of liver cells arranged on and abutting upon the central vein Between each of these plates of liver cells are small spaces (in reality the sinusoids) connecting freely with

the vascular idea has persisted and been supported by generations of micro-anatomists.

Kretz in 1905 studied thick serial sections of the liver and in man showed that normal liver cells form a continuous and connected mass He described the hepatic unit as follows, "The parenchyma of the liver surrounds the hepatic venous tree as a continuous mantle, while the portal vessels pervade the interstices between the cell mantles surrounding the hepatic venous radicles" Kretz agreed with Hyrtl who described the portal and hepatic veins as constantly crossing each other and so arranged that at all points they are separated by a layer of parenchyma In attempting to clarify his concept, Kretz likened the portal and hepatic vascular systems to two pine trees so carefully fitted together that each needle of one was separated from each needle of the other by a continuous layer of liver cells Kelly in this country, also in 1905, substantially confirmed Kretz's descriptions

The next investigator to elaborate on the minute anatomy of the liver was Epplen In 1922 he summarized his opinions as follows, "Essentially the liver is a radiation of two sets of capillaries arising from a common point [and] converging into the hepatic vein Since the liver is usually regarded embryologically as an epithelial structure, an adequate conception of its complicated vascular architecture cannot be obtained Indeed, it is just this that leads to the usual misconception of the anatomy of the lobule or acinus, described as it is as a rounded polyhedral mass of radiating cells with a central vein, surrounded by a connective tissue capsule. There are actually no such glandular lobules in the liver, each separate and distinct from its neighbor The liver is essentially a vascular skeleton in the interstices of which is a mass of cells, just like the flesh on a skeleton Hence, all parts of the liver tissue are not only in contiguity but in direct continuity with all other parts without complete connective tissue, separation or segregation into lobules" If, believes Epplen, there must be a lobule, it can be thought of with reasonable clarity as that mass of liver tissue enveloping a radicle of the hepatic vein It is punctuated and tunnelled by a fibrous capsule so that afferent blood is introduced into it at many different points Such a lobule would, of course, not "shell out" of a connective tissue capsule because it has none. In 1932 Arey reviewed all the evidence available and concluded that in reality the physiological unit of the liver is a composite structure composed primarily of the "peripheral parts of several adjoining lobules."

The anatomist most recently to attempt a detailed description of the hepatic lobule is Elias Particularly do Elias and his associates

1949

man and the cat, the spaces between the liver cells are wide and irregularly shaped, and the plates are broad ("hepar sacculare"). In the rabbit and the horse, the spaces between the liver plates are narrow and almost cylindrical ("hepar tubulare"), and in the dog a combination of these two types is found In Figure 35, the three basic structures of the liver—the cells, the sinusoids, and the large vessels—are combined to give a complete picture of hepatic structure

Although it can be granted that a concept of a hepatic unit is useful, some question can be raised as to its importance, for all of these units are, as far as it is known, identical The liver is not a structure like the pancreas with two types of units, the glandular

process quite generally involves the entire structure Because, however, it is difficult to think in terms of millions of cells and millions of vessels, and millions of ducts, some benefit accrues from retaining a concept identifying the liver as composed of innumerable functional units, any one of which will serve for the whole in a detailed study In the remainder of this section, an effort will be made to place within the empty spaces lying between the plates of liver cells the vascular and ductile components upon which each individual cell must depend for its existence and function

The Portal Venous System

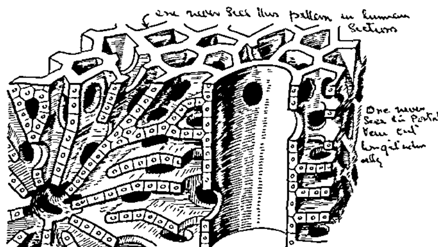
As soon as injection techniques were applied in the study of hepatic blood vessels, the basic pattern of the major and minor radicles of

course of the portal vein after its entrance into the liver As a result of their observations, they stated with assurance that the portal vein divides through six or seven orders of division until the sinusoids are reached Of particular interest is the fact that division almost uniformly takes place at right angles Recently investigators have reviewed the earlier studies, and a few pertinent observations have

slender branches which give rise almost immediately to the sinusoidal tufts In addition, blood is brought to the liver cells indirectly by way of small branches which ramify within the portal tract before

relationship in the following words, "If we split up a hepatic vein and examine its internal surface, we may see all over it a countless number of minute openings which belong to little venous twigs . . . The whole arrangement may be compared with that of the bristles in one of these brushes which are used for cleaning test-tubes."

As the periphery of the lobule is approached (i.e. where the liver plates abut on Glisson's capsule and the structures it contains), it



[illegible] arrangement of the liver cells is portrayed As in [illegible]

laminae radiate from the central space . The portal spaces (right), however, are lined by a 'limiting lamina' with which many intralobular laminae are connected The lacunae communicate individually with the central space [illegible]

Where a lobule rests against another lobule and not against the structure of Glisson's capsule, the plates of hepatic cells and their intervening spaces are continuous In Figure 34, the central and [illegible] complete picture of what [illegible]

Elias points out that there are species differences For instance in

reaching the point of sinusoidal division These slender branches are constricted near their origin, whether this is an artefact or a "true sphincter" Maegraith was unable to determine Free anastomosis between the branches of the portal vein was not noted except, of course, through the sinusoids. One of Maegraith's India ink preparations is reproduced in Figure 36 A.

Elias, in his analysis of the portal vein, confirms the observations of previous investigators concerning spatial relationships of the portal and hepatic systems One of Elias' plates (redrawn in Fig 36 C) clearly demonstrates branches of the portal giving rise to sinusoidal tufts as they run perpendicular to a central vein Of great interest is a slide (Elias 1949, Figure 15, page 433) made in 1887 by Stohr which shows distinctly by what means the sinusoid receives blood from the port[illegible]
terns of portal venou[illegible]
the limiting plate o[illegible]
into a sinusoid, (2) [illegible]

included Elias' final comments upon this new concept are "Thus, instead of hepatic cell 'cords' immersed in a mass of blood, the liver tissue consists of blood 'cords' embedded in a mass of hepatic cells The true liver structure is the diametric opposite of the old theory The conventional notion of the [illegible]

* In attempting to portray accurately Dr Hans Elias's concepts of hepatic [illegible]

[illegible] but extremely difficult to execute I have struggled with this same problem, but gave it up because I failed In supplying you with figures to replace yours, your original plan is abolished This is very [illegible]

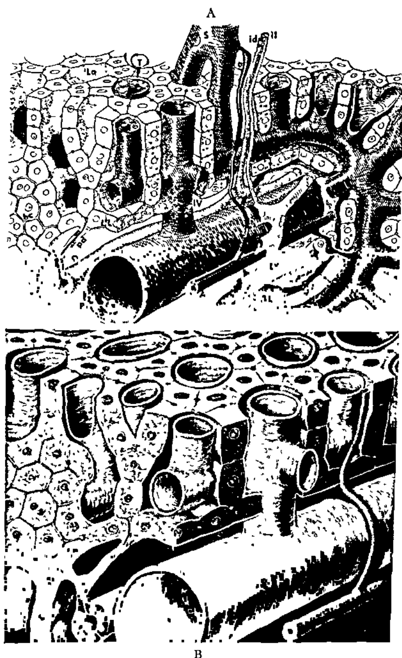


Fig 35 In this diagram* the components of the liver are assembled to-

the two main sites of entrance of the hepatic arterioles The bile ducts are also

because his injection mass was too viscid) the small venules which arise directly from the larger branches of the portal vein and run for some distance in Glisson's capsule before entering the sinusoidal space The subject of portal venous distribution cannot be closed

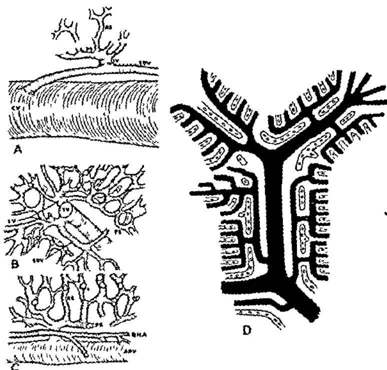


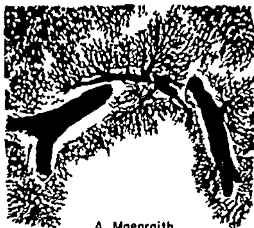
Fig 37 A and B Arising from a small portal vein branch (CV and TV) is shown a small distributing vein (SDV) From this arises an inlet venule (IV) through which blood gains direct access to the sinusoids (dog) C To the basic pattern of A and B has been added a branch of the hepatic artery BHA D Elias' schematic representation of intrahepatic branching of portal vein and portal venules The passage of the smallest vessels through the limiting plate to become, in effect, the sinusoids is clearly shown (From Elias Am J Anat, vol 85, 1949)

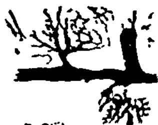
without mentioning the fact that certain branches of the portal vein and hepatic artery break up into a capillary bed surrounding the bile ducts This was first described by Kiernan and is most clearly shown by Maegraith in his illustration of a portal tract injected with Neoprene (Fig 38).

In summary, the present day anatomical concept of the terminal

lobule where it then breaks up into sinusoids. Actually, as these lie within the lobule, they might well be considered sinusoids rather than branches per se of the portal vein. In Figure 37 Elias' data on intrahepatic portal branching are summarized.

Although Mall stated on the basis of his original studies that capillaries (today identified as identical with the sinusoids) were given off only at their extreme tips, it appears that he missed (perhaps







drawn from Elias

distribution of the portal venous system favors the idea of short and long branches supplying the sinusoids (directly and indirectly) and the peribiliary plexus The venules supplying the sinusoids are presumed to have sphincters regulating the flow of blood to the sinusoid The picture of the portal venous system was static, that is, adduced from examination of microscopic sections, until Knisely, Bloch, and Warner threw additional and more dynamic light on this system by means of their transillumination technique. Knisely and his associates are primarily responsible for emphasizing the dynamic concept of the sphincteric activity in the venules described by Elias and Maegraith. This is located in the portal venules as they traverse the limiting plate to supply the sinusoid

The Hepatic Arterioles

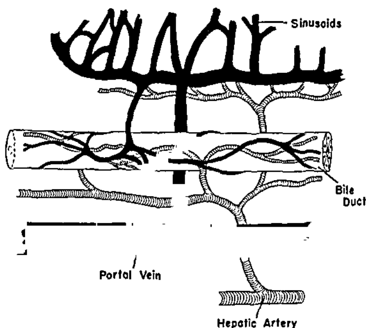
The manner of terminal distribution of the portal venules has been reasonably well understood for some time Precise and verifiable information concerning comparable relationships of the hepatic artery has only recently become available For somewhat over a century innumerable investigations and much discussion have centered about a single point how and where do the terminal hepatic arterioles join the sinusoids?

In 1833 Kiernan demonstrated small arteries lying within the walls of the portal veins and also forming capillary plexuses about the bile ducts Only rarely was he able to identify a few arterioles entering the lobules directly Gerlach (1849) and Mondine and Rattone (1889) supplied abundant evidence corroborating Kiernan's observations that the portal space is liberally supplied with branches of the hepatic artery In later years Pfuhl (1922), Loeffler (1927), Cameron and Mayes (1930), and Aunap (1931) also substantiated this aspect of intrahepatic arterial distribution None of these men, however, seemed able to set forth a clear concept of what happened to this arterial blood after it had passed through the capillary bed which they were all able to demonstrate in the portal space It was generally accepted that in one way or another collecting veins picked up the arterial blood and emptied it into the portal venules while these still occupied a position within the portal space.

Whereas Kiernan's writings have been widely read, those of Chrzonszczewsky seem to have been largely overlooked From the Department of Pathological Physiology in Charkov in 1866, this investigator published the results of his studies of livers injected with ammoniated carmine He wrote, "The lobules of such livers are separated from one another by the intralobular branches (of the portal vein) filled to the utmost with stagnated blood, next to these run numerous very fine branches of the hepatic artery stained red,

A





B

emptying directly into a fan-shaped cluster of sinusoids B Diagrammatic representation of peribiliary plexus (A, From Maegraith Ann Trop Med, vol 43, 1949)

though the quotation above is exact, it is impossible to find where Mall describes the arteriovenous junctions which he claims exist within the lobule A few years later, Gilbert and Villaret (1909) reported that as a result of their injection studies, they were forced to conclude that the bulk of arterial blood entered the lobule directly (not indirectly as Kiernan had implied) through a capillary bed draining into the portal venules in an extralobular position Again the actual junction of the hepatic artery and portal veins was not demonstrated

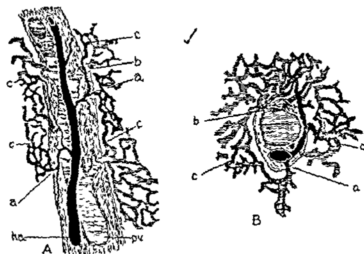
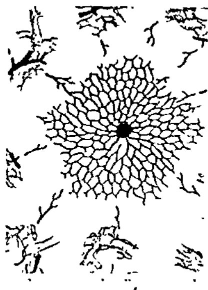


Fig 40 These two original illustrations of Olds and Stafford clearly demonstrate the peripheral entrance of the hepatic arterioles into the sinusoids. Incidentally, the portal venous entrance is also clearly shown (From Olds and Stafford Bull Johns Hopkins Hosp, vol 47, 1930)

The next investigators to study the hepatic artery seriously were Olds and Stafford In 1930, placing their faith in injection techniques, they attacked the problem of the "exact mode and site of junction between the portal venous and hepatic arterial trees" In microscopic sections prepared after suitable injection, Olds and Stafford were able to show that the hepatic artery communicates by means of arterial capillaries directly with the sinusoids at the periphery of the lobule They were unable, however, to demonstrate a connection between the hepatic artery and the portal vein within the portal space The branches of the hepatic artery which constitute the bile duct plexuses also appeared to communicate directly with

they course from the periphery to the center of the lobule and dissolve into the capillary network which takes up the blood too" Chrzonszczewsky's original Figure 5 is redrawn in Figure 39

In 1906 the American anatomist, Mall, apparently unaware of Chrzonszczewsky's earlier contribution studied the course of the

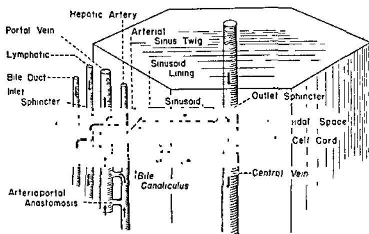


points out, many years ahead of his time (From Chrzonszczewsky Virchows Arch f path Anat, vol 35, 1866)

intrahepatic arterioles and concluded that their branches enter the lobules of the liver directly together with the branches of the portal vein and bile duct He wrote of the portal space, "Here the artery gives off a few branches to the bile ducts which form a capillary plexus around them, after which it communicates with the capillary plexus of the lobule By far the greater number of arteries enter the centers of the portal units and communicate at once with the capillaries, they supply the periphery of the lobules. . . . The great bulk of

hepatic circulation, Knisely's observations on the hepatic artery will be recorded in some detail In support of his method, Knisely pointed out early in his studies that a true picture of arterial flow cannot be derived from studies of histological sections of dead livers

Knisely believes that the hepatic artery gives off arterioles which course along the corresponding portal venule much like a vine on a [illegible]



[illegible]

branch of the hepatic artery Basically, then, Knisely has demonstrated that there are two types of connections arterioportal which lie within the portal space, and arteriosinusoidal which lie outside the portal space The degree of dilatation or of tonic contraction of the interlobular hepatic artery's arterioportal and arteriosinusoidal communications determines, of course, the composition of blood supplied to the liver cells When these are all tightly shut, the lobule receives only portal blood, when wide open and the portal sphincter closed, only arterial blood enters the sinusoid Various mixtures must take place between these two extremes as well as complete cessation of flow through a given sinusoid when both afferent sources are closed These mechanisms Knisely believes are under both nervous and hormonal control, but he admits that as yet precise knowl-

the hepatic sinusoids. In Figure 40 are reproduced Olds and Stafford's original illustrations Maegraith, some twenty years later, studied again the site of arteriovenous junction and concluded that in addition to supplying the tissues of the portal space, the hepatic artery sends branches directly to the peripheral network of sinusoids. In both instances, arterial blood mixes with venous immediately outside the portal space The bile duct plexus also drains directly into the sinusoid, not into portal venules

McIndoe summarized the extent of knowledge on the hepatic artery in 1928 by stating that he believed there was sufficient evidence to indicate a threefold distribution· (1) vaginal branches which supply the structures of the portal space through a capillary bed which then drains both into the portal vein and into the sinusoids; (2) vascular branches which enter the sinusoids directly; (3) capsular branches which communicate over the capsule with the phrenic, internal mammary, renal, and suprarenal arteries.

McMichael, who contributed so much in the 1930's to the problem of portal hypertension, reviewed all of the anatomical evidence and came to the conclusion that an arteriolar system is a practical necessity in order to reduce the arterial pressure to the level of that

the arterial and portal systems His techniques, which were physiological rather than anatomical, led him to conclude that the hepatic artery and the portal vein are linked in the portal tracts by an arteriolar capillary system.

Current thought on the hepatic artery is largely guided by the studies of Knisely, Mann, Maegraith, Elias, and Seneviratne. Beginning in 1932, Knisely and his associates started to develop their transillumination technique for the observation of living hepatic tissue. Most of their work has been performed upon frogs, but there seems little reason to believe that the circulatory dynamics of the mammalian liver is significantly different Furthermore, as the technique has been adopted by other investigators, mammalian livers have been studied and the original observations of Knisely on the frog liver have largely been confirmed Knisely's primary interest lay in attempting to determine the mechanism involved in selective phagocytosis To accomplish this aim, the liver was employed because of the relative ease with which its circulation could be observed In a sense, his observations and conclusions on hepatic circulatory dynamics were by-products of his major study. Because for the first time these reports produced a complete picture of intra-

Olds and Stafford's ... [illegible]

arteriovenous mixing took place in the portal canal, were unable to substantiate their beliefs experimentally Macgrath and his asso

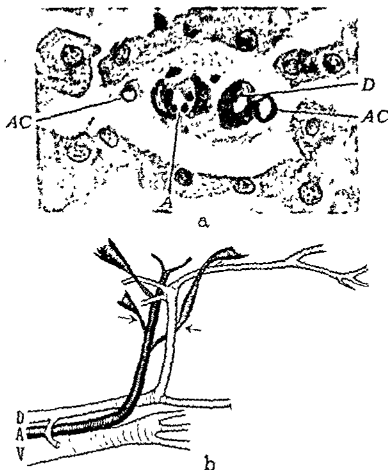


Fig 42 a Here is reproduced in cross section a small bile duct (D), an arteriole (A), and two arterial capillaries (AC) b From [illegible]

edge concerning their manner of action is not available In Figure 41 are combined several of Knisely's illustrations showing these relationships of the hepatic arterioles.

In 1942 Wakim and Mann, who used the transillumination techniques earlier employed by Knisely, published their observations on the circulation in the amphibian liver and in the liver of small mammals In both of these vertebrates a lobular pattern could be distinguished, though it was far more definite in the mammals than it was in the frog The lobules were uniformly arranged about a central vein One of the most striking features of circulatory activity was its intermittence, about 75 per cent of the intrahepatic circulation being inactive at any given moment. The volume of blood flow varied from minute to minute and from hour to hour In the frog, many arteriovenous communications could be found between corresponding branches of the portal vein and the hepatic artery. These actually took the form of shunts and were numerous. Just as often, however, the hepatic artery would wind around the portal, form a short loop, and then enter a lobule directly One feature of the frog's circulation which could not be identified in the mammalian organ was a definite communication between the hepatic artery and the hepatic veins In configuration these were similar to those between the artery and the portal vein Another feature of the hepatic circulation

into the substance of the lobule itself. Some of these emptied into the periphery of the lobule, while others coursed toward the middle of the lobule, terminating near the central vein These men also observed that certain sinusoids or even segments of sinusoids appeared to be supplied with blood either wholly arterial or wholly portal rather than a mixture In addition to the obvious *arteriovenous* communications within and without the lobule, Wakim and Mann described two types of venovenous communications, those occurring in the portal space and those located just as the portal venule is about to enter a sinusoid

times the size of capillaries into the portal vein and were able to retrieve them a few moments later from the lungs. They concluded, therefore, that there must be shunts of diameters comparable to

f the hepatic
nentally with

inability to reproduce Chrzonszczewsky's injection fluids. Elias fell back, then, upon the study of serial sections, and was able to show small hepatic arterioles present in the portal space These small, [illegible]

semblance to small bile ducts. In Figures 42 and 43 are reproduced Elias' reconstructions of several arterial capillaries. Here is shown an arterial capillary penetrating the limiting plate of the lobule (Fig 43) In many sections taken from the dog, the horse, and from man, arterioles and arterial capillaries have been traced for a considerable distance into the substance of the lobule (Fig 35). Elias, therefore, concludes that branches of the hepatic artery do supply the central areas of the sinusoids and that Chrzonszczewsky's observations, made nearly one hundred years ago, were indeed correct

As a corollary to his original observations, Elias points out that many of the intralobular capillaries are of very small diameter and by virtue of their small size act as sphincters entirely capable of [illegible]

contractility of the capillaries and bring hepatic blood flow under nervous control Elias indulges in some extrapolation when he states, "If it is closed, no arterial blood can flow," and likens the ends of these small capillaries to "nozzles of a garden hose" Unique is Elias' [illegible]

maintain that these arterial sinusoids can easily be distinguished from the conventionally described venous sinusoids or terminal [illegible]

ciates set as their primary objective the definition of the precise site where the arteriovenous mixing took place Their ingenious injection technique involved the use of two fluids which could be relied upon to form a precipitate on mixing one of these was injected into the hepatic artery, the other into the portal vein of small mammals. The precipitate was found in the large sinusoids immediately surrounding the portal tracts, in the vessels surrounding the bile ducts, in the

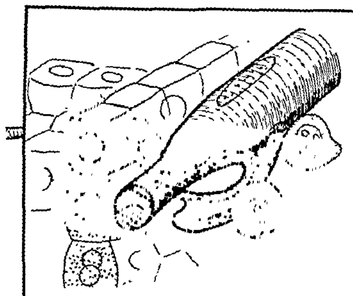


Fig 43 By assembling a number of sections of a secondary arterial capillary, Elias constructed this graphic picture of a primary arterial capillary giving rise to a secondary arterial capillary which pierces the limiting plate. The secondary arterial capillary is shown surrounded by three ganglion or glomus cells. The thickened wall of this tiny artery presumably represents a sphincter (From Elias Am J Anat, vol 85, 1949)

sinusoids radiating from the tips of the portal venules, and in small amounts in the branches of the portal vein

The anatomist currently expressing the greatest interest in hepatic structure in mammals is Elias This investigator gives Knisely full credit for providing essential information about the final distribution of the hepatic artery in the frog After reviewing the pertinent studies on the hepatic artery, Elias concludes that Chrzonszczewsky was correct when he contended that hepatic arterial blood gained access to the center of the hepatic lobule He tried to repeat Chrzonszczewsky's experiments but failed, attributing the lack of success to his

capillaries, he recognizes Kupffer's claim that these vessels are lined in part with stellate cells *Furthermore, Mall points out that it is* extremely difficult to find evidence of connective tissue within the liver lobule Both Oppel and Mall demonstrated by special techniques a fine reticulum comparable to that found in lymph nodes

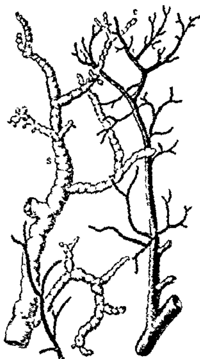


Fig 44 In 1906 Mall described the hepatic vein as larger than the portal and marked by many constrictions which formed "spiral valves" C represents a central vein, while S constitutes a sublobular vein (From Mall Am J Anat, vol 5, 1906)

and in other organs containing endothelial lined spaces Within the liver lobule, then, Mall defined three elements the liver cells, the endothelial cells (Kupffer), and a reticulum between them Mall admitted that the exact relationships between these elements were not clear

Minot was probably the first to recognize the importance of the conversion of a major vascular channel to a capillary-like vascular bed In the development of the liver, exactly this set of circumstances

the hepatic artery connects with the portal vein, with the sinusoids both peripherally and centrally, and with other branches of the hepatic artery. As had Wakim and Mann, Seneviratne demonstrated in the frog small arterial branches connecting with the hepatic vein which were not present in the mouse or rat. In general, Seneviratne felt that in the mammalian liver there were many types of communications between the hepatic artery and the portal vein and between the artery and the sinusoids. In summary, then, it can be accepted as proved with reasonable certainty that the hepatic artery, in addition to nourishing the structures of the portal space, communicates directly with the portal venules and with the sinusoids. These latter connections take place both at the periphery of the sinusoid and near its center.

The Sinusoids and Kupffer Cells

Although Malpighi, Glisson, Morgani, and other early microscopic anatomists recognized that the liver contained small blood spaces, they did not appreciate the exact nature of these vascular channels. For instance, in 1733 Ferrein described the lobules as composed of two different substances, one brown and the other yellow. He believed that these two differently colored areas indicated that the lobule was composed of cells constituting a true medulla and cortex. This view prevailed for over a hundred years, that is, until Weber proved that these variations in color were due to an unequal distribution of blood within the lobule. To Kiernan the medical world owes its first accurate description of the small blood vessels distributed throughout each lobule. As related earlier, Kiernan described practically all of the intrahepatic structures. The intralobular vessels he termed capillaries. When, in 1899, Kupffer described the stellate cells which now bear his name and which he thought lay within the intralobular capillaries, all of the essential constituents of the blood vascular system separating the liver cells had been identified.

Mall, in 1906, published his extensive monograph on the structural unit of the liver. In this he gave a most comprehensive description of the capillary bed of this organ, and his illustrations of these small blood vessels leave little to be desired in the way of clarity. For instance, Mall's Figure 32 which outlines in detail intralobular capillary architecture has not been improved upon since its publication a half century ago. This is reproduced in Figure 44. Mall also commented at length upon Thoma's principles of capillary bed development and their application in the liver. Although in the greater part of Mall's writings he refers to the intralobular vessels as

capillaries, he recognizes Kupffer's claim that these vessels are lined in part with stellate cells Furthermore, Mall points out that it is extremely difficult to find evidence of connective tissue within the liver lobule Both Oppel and Mall demonstrated by special techniques a fine reticulum comparable to that found in lymph nodes

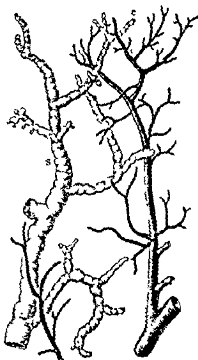


Fig 44 In 1906 Mall described the hepatic vein as larger than the portal and marked by many constrictions which formed "spiral valves" C represents a central vein, while S constitutes a sublobular vein (From Mall Am J Anat vol 5 1906)

and in other organs containing endothelial lined spaces Within the liver lobule, then, Mall defined three elements the liver cells, the endothelial cells (Kupffer), and a reticulum between them Mall admitted that the exact relationships between these elements were not clear

Minot was probably the first to recognize the importance of the conversion of a major vascular channel to a capillary-like vascular bed In the development of the liver, exactly this set of circumstances

prevails As the liver cells pervade the omphalomesenteric veins, these vessels are converted to a capillary-like bed which differs in a number of respects from a capillary bed as the term is generally used For this reason, Minot suggested the term sinusoid, designating the circulation through such vessels as sinusoidal Based largely on Minot's concepts, the vascular spaces lying between the plates of liver cells have come to be called sinusoids rather than capillaries

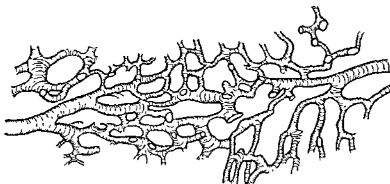
Minot takes pains to point out that a sinusoid differs in many important respects from a true capillary, although its walls also consist of endothelial cells without any supporting media or adventitia. A sinusoid, according to Minot, is of larger caliber and its cells are applied closely against the cells of the organ in which it has developed Furthermore, its walls present innumerable large apertures through which it intercommunicates freely with neighboring sinusoids It follows the architectural pattern of the organ in which it resides, it does not, as does the capillary, follow its own pattern. The sinusoid is not, as is the capillary, imbedded in connective tissue. In addition, the embryological development of the sinusoid differs fundamentally from that of the capillary. All of Minot's criteria for a sinusoidal circulation are fulfilled in the circulation of the hepatic lobule The basic reason, of course, for the close proximity of the sinusoidal wall to the liver cell lies in the assumption that efficient parenchymatous function is thereby greatly facilitated.

For the next thirty to forty years, little was added to Minot's and Mall's fundamental description of the hepatic capillaries or, as they have come to be designated, the sinusoids. Such comments as were made during this period were based upon examination of fixed liver tissue Epplen simply refers to these vessels as capillaries, Rolleston and McNee dismiss the subject by stating that the portal capillaries are peculiar for their width and their incomplete lining with Kupffer's cells The articles of Olds and Stafford, Maximow, and others writing in the 1930's reflect a more complete appreciation that the lobular vessels are not simple capillaries From approximately this time on, the term sinusoid has been used extensively and its connotations incorporated into all thinking on the vascular components of the liver

Present concepts of the anatomy and physiology of the hepatic sinusoid have largely been developed by Knisely, Mann, and more recently by Elias The first two worked with the transillumination technique, while Elias has relied largely upon examination of serially cut histologic sections of the liver Although most of Knisely's observations were upon frogs' livers, others have confirmed his findings in so far as small mammals are concerned (Hoerr, Soskin, Essex, Herrick and Mann) Early in his description of the sinusoid, Knisely

[illegible]

through [illegible]." He describes the sinusoids of the frog's liver as "smooth walled, branching and anastomosing cylindrical tubes, which have a complete cellular lining. Each cell of this lining is a phagocytic von Kupffer cell." Knisely agrees with Ellinger and Hirt who, in 1929, showed that the cylindrical configuration of the hepatic sinusoid could be nicely outlined after injection of fluorescent dyes He insists that the Kupffer cell is never suspended like a spider in



[illegible]

hepatic portal vein, Elias described the sinusoids from the histologist's point of view "At their very tips," writes Elias, "the portal vein branches split up into sinusoids These terminal ends of the portal vein anastomose with their own kind via the sinusoids" Elias' Figure 21 which is reproduced in Figure 45 shows his concepts of the intralobular circulation very clearly According to him, the terminal twigs of the portal venule enter the lobule in either of two general ways, as end arborizations supplying the periphery of the lobule or as axial sinusoids which run deeper into the lobule before splitting up into branches All variations on these two general patterns, of course, can be identified Elias states that basically he is in agreement with Knisely's concepts In support of certain minor differences, he points out that the fixed slides he was studying can be

prevails. As the liver cells pervade the omphalomesenteric veins, these vessels are converted to a capillary-like bed which differs in a number of respects from a capillary bed as the term is generally used For this reason, Minot suggested the term sinusoid, designating the circulation through such vessels as sinusoidal Based largely on Minot's concepts, the vascular spaces lying between the plates of liver cells have come to be called sinusoids rather than capillaries.

Minot takes pains to point out that a sinusoid differs in many

s of the organ in which it has de-

In addition, the embryological development of the sinusoid differs fundamentally from that of the capillary. All of Minot's criteria for a sinusoidal circulation are fulfilled in the circulation of the hepatic lobule The basic reason, of course, for the close proximity of the sinusoidal wall to the liver cell lies in the assumption that efficient parenchymatous function is thereby greatly facilitated.

For the next thirty to forty years, little was added to Minot's and Mall's fundamental description of the hepatic capillaries or, as they

cells The articles of Olds and Stafford, Maximow, and others writing in the 1930's reflect a more complete appreciation that the lobular vessels are not simple capillaries From approximately this time on, the term sinusoid has been used extensively and its connotations incorporated into all thinking on the vascular components of the liver.

Present concepts of the anatomy and physiology of the hepatic sinusoid have largely been developed by Knisely, Mann, and more recently by Elias The first two worked with the transillumination

Herrick and Mann) Early in his description of the sinusoid, Knisely

efforts he was unsuccessful, and today the smallest branches of the hepatic veins, the central veins, are accepted as the axis of the somewhat poorly circumscribed hepatic unit, the lobule

As a result of his painstaking injection technique, Mall pointed out certain anatomical differences between the portal and hepatic veins The latter are somewhat larger and possess fewer terminal twigs In the dog and the cat, they present a peculiar spiral pattern, the significance of which has never been determined although it is [illegible]

portal vein connects with the sinusoid only at its tip, whereas the hepatic vein not infrequently receives sinusoidal drainage directly into its larger branches (See Fig 44)

To the anatomists, then, the hepatic veins presented themselves as an uncomplicated system of vessels draining the liver without structural details indicative of any particular function When physiologists became interested in the various responses of the liver to stimuli of one sort or another, the hepatic veins began to acquire a measure of functional significance Bauer, Dale, Poulsson, and Richards called attention to the strong bundles of smooth muscle in the caval ends of the hepatic veins of the dog To a sphincter-like action of this musculature these investigators as well as others (Simonds, Popper) ascribed certain unusual ways in which the dog's liver responds to a number of different drugs Deysach also became interested in the function of the hepatic veins and reported that in the animals which they had studied (dog, raccoon, opossum, bear, and others), the junction of the sinusoids with the central veins was the site of a "sluice-like valve mechanism" They believed that this mechanism, which was under drug, hormonal, and nervous control, accounted for the behavior of the liver under a variety of circumstances They also pointed out that the central veins as well as the smaller branches of the hepatic veins possess contractile qualities which could control the volume of fluid either impounded in the liver or released from it into the general circulation Knisely, following this trend, expressed the belief that the outlet sphincters of the sinusoids together with Deysach's "sluice mechanism" functioned importantly in enabling the liver to carry on the role of a blood reservoir The peripheral red cell count, the circulating blood volume, the venous pressure, and the cardiac output could all be materially affected by these valves which so effectively control sinusoidal emptying In precise anatomical detail, the hepatic venous tree can then

compared with a "snapshot of a transitory phase which exists only for a very brief period." In final analysis, Elias believes it quite possible that the two types of sinusoidal patterns which he describes are simply a manifestation of the contractility of sinusoids so extensively emphasized by Knisely.

Next to the liver cells, the Kupffer or stellate cells are the most important cellular component of the liver The special cytology of these cells was ably reviewed by Mann in 1932 He expressed the belief that phagocytic activity characterizes the functionally active Kupffer cells As blood passes through the liver, it is readily freed of foreign particles through the activity of these cells. The mechanics involved in this process were the basis for Knisely's extensive studies on selective phagocytosis published in 1948 Knisely summarized his opinions at the Ninth Macy Conference on Liver Injury somewhat as follows: The stellate cell of Kupffer does not ingest every foreign particle which enters the hepatic sinusoid Selectively, foreign particulate matter receives a coating of a clear, glossy precipitate, prob- [illegible]

[illegible] rived from studies of the hepatic circulation in living livers that the older idea that the sinusoid is composed of two cells, endothelial and stellate, should be abandoned

The Hepatic Venous Drainage System (Hepatic Veins)

Although difficulties and complexities beset investigators studying the hepatic artery, portal vein, and hepatic lymphatics, those inter- [illegible] -em to have experienced [illegible] portion of the hepatic [illegible] the central vein as the axis of the hepatic lobule and the hepatic veins and their branches as the blood drainage system of the liver retains its validity today Although Mall accepted Kiernan's work on these vessels, he proposed, a number of years later, that the unit of the liver be oriented about the smallest branches of the portal vein as its center. In these

injection masses employed has penetrated the lobule. Even today the precise architecture of the intralobular lymphatics remains undefined

The first important morphological observation upon the intralobular lymphatics is that of MacGillavry who in 1865 described a clear narrow space between the wall of the sinusoid and the membrane of the liver cells Thirty years later, Disse described this same space, and for some unexplained reason this area, described first by

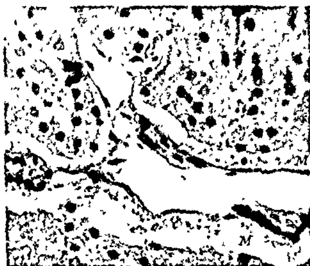


Fig 47 Elias' concept of Disse's space which has been referred to here as Mall's space and designated by the letter M (cat) (From Elias Am J Anat, vol 85, 1949)

MacGillavry and later by Disse, is now known as "Disse's space" Perhaps no histologic entity has been the subject of more extensive discussion. From time to time, the concept of Disse's space has fallen into disrepute, for many investigators maintained that it was an artefact consequent to tissue fixation

Mall, in 1906, asserted that he was able to inject the lymphatics successfully by employing Prussian blue gelatin He stated that the blue entered the capillaries of the lobule and was thence filtered through the capillary
lobular" lymph space
fined as communicat
with a large lymph space between the liver cells and the capsule of Glisson " These spaces intercommunicate with the lymph radicles lying within Glisson's capsule Mall's Figure 54 is reproduced in

be considered a relatively uncomplicated system of veins without evidence of communication with the other circulatory systems of the liver other than through the sinusoids.

The Hepatic Lymphatics

The story of the relationships of the liver to the lymphatic system is long and complicated, and the last chapter has yet to be written Henry has ably reviewed the historical question of who discovered lymph channels It was not for some years after Asellius (1627) described the lacteals that Jolyff was credited by Glisson with having

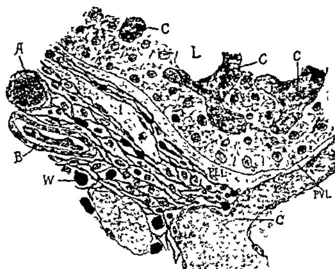


Fig 46 Mall's illustration depicting the much discussed Disse's space PVL, so designated to represent the perivascular lymphatic space, has been presumed but never proved to function as the intralobular lymphatics (From Mall Am J Anat, vol 5, 1906)

found lymphatics within the liver (1650). At about the same time, Pecquet (1647) and Rudbeck (1651) independently described the thoracic duct. It was the discovery of the lymphatic system which dealt the time-honored views of Galen a crippling blow Here were channels through which products of digestion were carried to the

tained. Injection techniques served admirably to demonstrate the lymphatic vessels in the portal spaces, but none of the translymphatic

fold first, to salvage plasma protein, and second, to conduct stored and newly formed protein to the general circulation In the normal dog, the volume of lymph secreted per twenty-four hours was found to amount to 47 per cent of the estimated plasma volume This contained 35 per cent of the total circulating plasma proteins In experimental cirrhosis, the flow of hepatic lymph was found to increase as much as 258 per cent and to contain as much as 207 per cent of the circulating plasma proteins The rate of flow under these circumstances was accelerated as much as 500 per cent In patients with cirrhosis, a tremendous increase in lymph flow leaving the liver can legitimately be postulated upon the hugely dilated lymphatic channels which can be seen about the porta hepatis during surgical operations for portal decompression This pooling of lymph is not seen during operations about the porta hepatis of patients with normal livers

In association with experimental cirrhosis, Bollman and his associates became interested in the intricate relationships of the lymphatics with the blood supply to the liver At the Ninth Macy Conference on Liver Injury, Bollman reported the results of his study and the discussion which his remarks initiated indicates the confusion which exists concerning the intrahepatic lymphatics Bollman's first observations were upon retrograde India ink injections into pigs and rats In general, it was demonstrated that the hepatic lymphatics follow the portal vein down to its finest terminal venules, but ink could not be found within the hepatic lobule proper If perisinusoidal lymph spaces exist, they were not injected by this technique A few lymphatics surrounding the hepatic veins could be identified as well as a rather extensive network surrounding the bile ducts As a random comment, Bollman called attention to the well known experiments in which occlusion of the common bile duct is followed in a matter of minutes by the appearance of bile in the hepatic lymph He then remarked that it appeared to him that the lymphatics are the chains forming a mechanism for fluid and solute

Figure 46. Both Disse's space and Mall's space have been identified histologically by Elias, and in his Figure 40, which is reproduced in Figure 47, a
hepatic lymp
temptation to refer to these two spaces as lymph spaces or channels Although they may function as such, they can never by definition be true lymphatics, for they do not possess endothelial linings The perisinu
the sinu
cells an
(Mall)
tract an
Mall would, he could not demonstrate histologically any direct connection between his space and the readily identifiable lymphatic channels lying within the portal spaces. Mall concludes, "All my

"rapid transfusion through them "

Knisely, in his innumerable observations of the living sinusoids of the frog, Wakim and Mann in their studies of the livers of small mammals, and Bloch in his observation on the sinusoids of rhesus monkeys, have all concluded that these spaces must function in a

amounts of fluid leave the liver. None of this ever appears in the central venous system, or in the bile ducts, nor does the liver swell Knisely maintains, therefore, that this large volume of fluid must pass out through the only other exit available, the lymphatics.

Recently Popper has questioned again the actual existence of the perisinusoidal spaces of Disse He bases this doubt primarily upon sections of liver obtained from persons dying instantaneously in which Disse's space could not be found When, however, death was preceded by an agonal period, this space appeared in the microscopic sections Popper concluded, therefore, that Disse's space is an artefact

Cain, who demonstrated that the hepatic lymphatics could be intubated, started a series of investigations which promised to help clarify the problem of hepatic lymph drainage. Nix and his associates, in their studies on the dog, showed that the liver contributes the bulk of the fluid and protein content of the thoracic duct. Since

CHAPTER 7

The Normal Physiology of the Hepatic Vasculature

HISTORICAL NOTE

UPON what evidence Galen based his conclusions that the liver was the site of sanguinifaction is not at all clear, but he must be credited with the first attempt to solve many of the problems of the physiology of the liver After him came the centuries of purely anatomical investigation, the highlights of which have been reviewed in the previous chapter To identify precisely when anatomical investigation gave way to physiological is difficult, for no sooner were anatomical observations recorded than efforts were made to interpret these in terms of function For instance, Glisson, after describing the portal space and its contents, postulated that the parenchyma of the liver served [illegible]

Dier [illegible]
liver as [illegible]

a certain Strainer through which the Blood and Humours pass, and that those alterations which they undergo in the Liver are accomplish'd by percolation True it is, such a simple straining may separate the thin from the thick, but occasion no other alteration worth [illegible]

through, losing its own nature and sweetness, is chang'd into bitter and yellow Choler If Glisson should perhaps object, That that same Choler is the thicker part, and therefore it does not pass with the rest of the blood but is evacuated through the Ductus Biliarius, I answer, That the Choler indeed does often acquire a certain thick- [illegible]

blood itself And this I will prove by the Roots of the Porus Biliarius,

remarks, he emphasized again that although large fluid exchanges are known to occur, technical advances have not yet permitted final settlement of the precise mechanisms through which these exchanges are mediated. At the moment, then, it can safely be stated that the last word has not been written on the hepatic lymphatics.

tral vein. Near the periphery these appeared primarily to be bifurcations, while at the center of a lobule they seemed to appear as reanastomoses. The main purpose of both sets of sphincters seemed to be to control the rate of blood flow through the lobule. As the intralobular circulation was observed over a period of time, these sphincters could be seen in all phases of contraction and dilatation. At certain times they were widely opened, at others they were partially patent, and at still others they appeared to be shut tightly.

Knisely summarized the modern concept of intrahepatic vascular activity as follows, "The terminal hepatic arterioles, the arterial sinus twigs, the terminal portal venules, the arterioportal anastomoses, the inlet sphincters, the tubular sinusoid linings, the outlet sphincters of the sinusoids and of Deysach's small sluice channels, the central [illegible]

[illegible]

[illegible]

When the hepatic vessels are considered as a whole, it is obvious that the most important single unit is the capillary bed or the sinusoids. The hepatic artery brings arterial blood to the liver, the portal vein brings portal blood from the spleen, pancreas, and gastrointestinal tract, while the hepatic veins basically constitute a drainage system for the liver. It is obvious that these large vessels occupy space and are subject to the usual vascular controls, yet their total activity is small compared with that of the sinusoidal bed. When these great vessels are taken as a whole, they are found concerned primarily with transporting blood to and from the liver. Together with the sinusoids, they create a "milieu intérieur" for the liver cell such as that postulated for the body's cellular structure as a whole by Claude Bernard.

Any study of the function of the hepatic vasculature must be concerned primarily with the mechanisms by which the blood vascular tree creates and maintains a suitable medium for hepatic cellular activity. In addition to this its major function, it is generally con- [illegible]

and the Gall-bladder, which are much less, much thinner and narrower than the Roots of the Vena Cava inserted into the Liver. For if it were thicker, it could never be suck'd in and evacuated through the Vessels much thinner than the rest; and leave the thinner to be receiv'd by the bigger and larger Roots of the hollow Vein. Besides, the Choler sweats through the Tunicles of the Gall-bladder, and dyes the neighboring Bowels of a yellow colour, whereas, the blood never sweats through any Tunicles of the Veins, which are thinner and softer than that Bag; and this is very likely to be true, because it is much thicker Therefore, the true office of the Liver is to moisten the Blood with a sulphury Dew, and together with the Spleen to perfect the ferment of that and the Chylus. And therefore all Men, all Creatures, as well as by Land as by Water are furnish'd with the liver, because without that Ferment the spiritous blood could never be made "

Amusing as this bit of armchair physiology may be, it typifies the early history of the development of knowledge concerning the function of the hepatic blood vessels Gross and microscopic anatomists alike have many times attempted to draw physiological conclusions from the study of dead and fixed tissue. At the Ninth Macy Conference on Liver Injury, Knisely chid these investigators with, "Histologists like to believe they can stain everything in tissue. That is not so They believe if something is made out of smooth muscle, it could contract, and if not, it could not contract. There are things in animals which can contract which are not made of simple smooth muscle "

MODERN CONCEPTS

Today a new chapter in hepatic physiology is being written, not through the study of fixed and stained sections of liver, not through indirect evidence based upon gross physiological observations, but upon actual observation of living tissue From the dynamic picture presented by the transillumination technique, Knisely, Mann, Seneviratne, and others have been able to verify many of the complex vascular mechanisms *postulated by the microscopic anatomists of* the past For instance, Knisely has identified an inlet sphincter at the junction of the portal venule with the portal vein Furthermore, he has seen an outlet sphincter located at the junction of the sinusoid [illegible]

[illegible]

sisted of several confluent sinusoids with a common outlet to a cen-

sinusoidal bed Although clearly demonstrated only in the dog, it seems logical to believe that man, too, is able to control hepatic blood flow by means of smooth muscle located in the walls of the hepatic veins as these enter the vena cava

Although the liver itself may have a limited capacity in terms of volume as compared to the spleen and the vessels of the gastrointestinal tract, the amount of blood under control of the various hepatic gate-like mechanisms is large. Under ordinary circumstances the hepatoportal system may hold as much as 55 per cent of the total blood [illegible]
nisms [illegible]
from [illegible]
means complete master of its own circulation

INTRAHEPATIC AND EXTRAHEPATIC VASCULAR OCCLUSIONS

For many years the gross effects upon the liver of occluding the major vessels entering or leaving it have been well known Sudden occlusion of the portal vein produces a temporary shrinkage in hepatic volume without change in color Within a few minutes, however, the size of the organ returns to normal When the hepatic artery is suddenly occluded, there is little discernible change in volume Upon occlusion of both the hepatic artery and portal vein, the liver shrinks, becoming flaccid and dark in color Occlusion of the hepatic veins produces a tremendous congestion of the liver as both portal and arterial blood are poured into it without a pathway for [illegible]

When Knisely, Wakim and Mann, and Seneviratne observed the intrahepatic circulation through the microscope, the effects upon the sinusoids themselves of these various occlusions could be studied Early in the course of Knisely's original observations, he noted the effects on sinusoidal blood flow of closure of various of the hepatic vascular channels. During obstruction of the outlet venules of a sinusoid, he was able to observe great distention of an individual lobule, where hepatic arterioles were closed, the related sinusoids received only portal blood Conversely, when portal venules were tightly closed, only arterial blood flowed through a given set of sinusoids

On the basis of their studies, Wakim and Mann expressed the belief that the relationships described by Knisely were *not wholly* correct They thought they were able to demonstrate that whole sectors of liver were supplied predominantly with arterial or with portal blood When these investigators occluded the hepatic artery,

large volumes of blood which it can release on demand. Compared to the activity of the sinusoids in relationship to hepatic cellular function, these other activities are all but negligible.

THE BLOOD RESERVOIR FUNCTION OF THE LIVER

With the spleen, lungs, and subcapillary venous plexus of the skin, the hepatic vessels have long been known to participate in the function of blood reservoir Although the percentage of blood volume stored and released by the liver varies considerably from species to species, it is generally conceded for all mammals that the liver dilates whenever the return of blood to the heart is excessive. Conversely, the liver is able to discharge considerable amounts of blood to maintain cardiac output under emergency conditions Gollwitzer-Meier,

vena cava increased Schutz showed that in cardiac failure, blood may account for as much as 60 per cent of the weight of the liver. Ludwig estimated that the liver of a normal man could deliver as much as 1 to 2 liters of blood on demand More recently Bradley and his associates, after establishing the validity of estimated hepatic blood flow by Bromsulphalein retention, showed that the flow of blood through the liver varied greatly during vasoconstriction and ... emergency reactions splanchnic flow was aug-

many times that the liver as well as the portal system has a distinct part in regulation of general blood flow

Most of the evidence has been obtained from animals, but there is sufficient correlation with man to support the belief that, though variations in degree may be present, the basic mechanism is the same Under various conditions, considerable amounts of blood and fluid may be removed or returned to the general circulation by several means described by various investigators Wakim and Mann, patterning their experiments after Knisely's observations on the frog, have demonstrated that periods of increased and decreased blood

would happen were small intrahepatic portal venules occluded. To this end, he injected a suspension of starch granules in 5 per cent gum acacia (particle size 5 4 microns in diameter) When a small quantity of this material was injected slowly, the intrahepatic circulation did not change dramatically, although large granules could be seen obstructing a short segment of the sinusoid If large quantities of this material were injected, the sinusoids and portal venules became plugged, and the portal circulation came to a standstill Child and Barr, in their experiments with beryllium oxide, have shown that this material can plug the sinusoids to such an extent that in the dog effective portal occlusion is accomplished In such experiments, the portal pressure rose to 40 to 50 cm of saline, and the dogs died With smaller amounts, the portal hypertension was transient, and the animal recovered

BLOOD FORMATION AND DESTRUCTION IN THE LIVER

Only in embryonic life does the liver function as a blood-forming organ Few subjects in histology have been the object of greater controversy than those concerned with the origin of the formed ele-

[illegible]

poiesis begins with the "rounding up of outstretched mesenchymal cells into free basophil cells which in time give rise to all types of blood cells" Initially, this takes place in the yolk sac, then successively appears in the body mesenchyma, the liver, the bone marrow, the spleen, and the lymph nodes From the very beginning of the formation of the liver, large thin-walled blood vessels are located in a meshwork of developing epithelial cells A thin layer of mesenchyma lies between the vascular endothelium and the hepatic epithelium From these mesenchymal cells arise the hemocytoblasts which proliferate hemopoietically to form, in the extravascular position, erythroblasts, megalokaryocytes, and myelocytes The mature erythrocytes are believed to slip through the walls of the sinusoids to enter the general circulation

At about this time, the endothelium of the sinusoids is transformed into a layer of macrophages which form the Kupffer cells in the adult liver Here, then, is one of the essential metamorphoses of the hepatic vascular system upon which later depends one of the major functions of the liver, phagocytosis Although the sinusoids originally are lined by endothelium, this is largely replaced very early in embryonic development by a specialized cell having a specific function Whether the transformation from endothelial to Kupffer cell is complete or not is still undecided Knisely maintains that in

When a branch of the portal vein was closed, blood stopped flowing in the sinusoids which Wakim and Mann believed to be supplied

the systemic injection of India ink that small amounts of blood continue to reach the liver by way of arterial collaterals (internal mammary, diaphragmatic, and deep hepatic) and by way of blood regurgitating up the hepatic veins

Seneviratne extended these observations, paying particular atten

sulted in appreciable slowing of the circulatory rate in the portal and hepatic veins This was only temporary, for within two or three minutes circulation returned to normal. The important implication here is that in both of these animals there are sufficient intrahepatic arteriovenous anastomoses to return lobular blood flow to normal within a very short time Seneviratne was unable to distinguish important circulatory differences between the frog and the rat after occlusion of the hepatic artery; in both animals, blood flow diminished and then promptly returned to normal In a measure, these observations confirm those of earlier investigators who demonstrated a very real degree of reciprocity between the liver's two sources of blood, the portal vein and the hepatic artery

empty of blood A few minutes later, the central portions of the sinusoids became partially filled with blood This was interpreted by Seneviratne as back flow from the hepatic veins Obstruction of the hepatic veins produced intense sinusoidal and vascular congestion and apparent complete arrest of the circulation.

From the clinical point of view, Seneviratne's observations on

lation to the normal liver could be adequately maintained by the hepatic artery alone. Seneviratne also became curious about what

healthy erythrocytes As the coated particle enters the sinusoid, it immediately manifests a strong tendency to adhere to the sinusoidal wall Tethering of a particle by its streamers may enhance this process but is not necessary As soon as a coated particle sticks to the wall of a sinusoid, it sinks, streamers and all, into the cytoplasm of the first mural cell with which it comes in contact. The volume of the Kupffer cell ingesting such a particle increases That this is a selective process is shown by the fact that normal red and white cells bump along from side to side in the sinusoid without showing the

tion of thorium dioxide, for instance, this substance can be demonstrated within the Kupffer cell. However, when silica is injected, much of this material finds its way into the lymphatics of the liver and can be identified in large amounts in the nodes draining the liver

Acacia, one of the colloids which was for years considered a satisfactory blood substitute in the treatment of shock, persisted in the liver and interfered seriously with liver function Mannix and others have demonstrated that arabinosis is a strange disease of the liver which follows the intravenous injection of acacia Macromolecular substances such as these do not easily pass through the capillary walls but are stopped by the phagocytic cells of the liver Patients who have received acacia may present many years later greatly enlarged livers

substances are being studied intensively as potential blood or plasma substitutes Whether these will ultimately be found to have a deleterious effect upon the liver has yet to be determined Dextran, a polysaccharide of high molecular weight, has been used extensively in studies on shock and found to exert a beneficial effect upon this state, ultimately this material is completely metabolized Polyvinyl pyrrolidone has also been employed as a plasma expander It too ameliorates the shock state, but microscopic examination of the lymph nodes, liver, and spleen of animals receiving large doses of this substance reveals that important amounts are taken up by the reticulo-endothelial system and apparently remain there permanently (Kellner) Whether the presence of this substance in the animal's lymphatic system as a whole is harmful has not yet been determined

Nor is the reticulo-endothelial system of the liver restricted entirely to phagocytic activity Lasch and Roller have shown that when the Kupffer cells are blockaded by particulate matter, the liver's ability to store vitamin A is greatly reduced This fact is of consid-

the adult the sinusoid is a cylindrical tube completely lined by Kupffer cells. Maximow and Bloom, on the other hand, describe two types of cells lining the sinusoid, the endothelial and the Kupffer cell These authors state, however, that "numerous transitional forms connect these two cell types" Evidence that these are all one and the same cell is derived from the fact that the larger the amount of vital dye introduced into the liver, the greater does the number of these phagocytes appear to be By the end of intra-uterine life, hemopoietic activity in the liver has largely ceased

PHAGOCYTIC ACTIVITY OF THE SINUSOIDS

As soon as early anatomists appreciated that the liver received all of the blood draining the intestinal tract, they assigned this organ a scavenger action So generally was this concept accepted that for many years the liver was actually referred to as the body's cesspool In the performance of this function, the liver was likened to a "strainer" Teleological as were these early concepts, they were not far wrong, for in recent years many have demonstrated the liver's remarkable capacity for removing a wide variety of substances from the blood stream

It has been shown that by means of the phagocytic activity of the Kupffer cell particulate matter, certain colloids, worn out red and white cells, and many types of bacteria are removed from the blood stream India ink, silica, and other small particles are extracted from the blood stream in the liver Drinker and Shaw have shown that manganese dioxide can be completely removed by the end of twenty-four hours after injection Roger demonstrated that animals survive many times the lethal dose of certain bacteria provided these are injected into the portal blood stream rather than into a peripheral vessel One of the techniques for producing extensive scarring of the liver involves the repeated injection of highly irritating materials [illegible] ist [illegible] iat

In their extensive studies on selective phagocytosis in the frog's liver, Knisely, Bloch and Warner have worked out in great detail how this process takes place Immediately upon its introduction into the blood stream the small particle (India ink) acquires a coating, [illegible] from that of plasma [illegible] identified under the [illegible] to identify the exact nature of this coating, but several of its features became obvious in the course of their studies. This coating frequently leaves streamers behind, and it does not form about normal blood elements such as

of physiological obstruction lay, therefore, on the hepatic venous side of the liver and that as fluid was removed from the portal circulation it was stored in the liver temporarily. Slowly it found its way back to the general circulation by way of the hepatic lymphatics and thoracic duct. Thus, sudden overloads of water can either be selectively stored in the liver or returned to the circulation. Nor need an overload of fluid be derived from water administered intravenously. For years it has been recognized that large amounts of water enter the portal system daily. In its hydrodynamic role, the liver concentrates the dilute blood brought from the gastrointestinal tract. Part of the excess fluid is returned to the general circulation slowly by way of the hepatic lymphatics, while part is excreted through the biliary tract.

Although these gross mechanical aspects of water regulation have been known for years, the exact mechanisms by which the liver accomplishes this function were not studied until direct observations upon the liver could be made. Again Knisely, Mann, Seneviratne and others are largely responsible for information, controversial as it is, on this phase of hepatic vascular activity. As a result of many hundreds of observations upon frogs' livers, Knisely finally came to the conclusion that there are three phases of permeability of the sinusoidal membrane. In one phase, he noted that the red cells changed their relationship to their fluid menstruum but little. Here he concluded that little if any fluid was leaving the sinusoid. At the opposite extreme is the second phase during which the red cells become closely packed as they traverse a given sinusoid. During this phase, Knisely believes that the sinusoidal membrane is extremely permeable to water and to blood colloids. This phase he has described as one of "continuous filtration," and it is one during which large amounts of water and blood colloids (primarily plasma) pass out into the lymphatics. This hypothesis, of course, confirmed the experimental observations of Starling, of Drinker, and of McCarrell and Drinker who noted that under various circumstances the liver of cats and dogs can and does form large amounts of lymph which contains about as much protein as blood. The third phase of permeability Knisely described as intermediate between the two extremes just noted. Seneviratne, on the other hand, in his studies on the liver was unable to confirm Knisely's observations. He agreed that the sinusoid represented a continuous thin tube, but he could not identify the valves upon which Knisely bases so much of his interpretation of hepatic circulatory dynamics. Nor could Seneviratne identify Disse's spaces. This investigator, therefore, could not confirm entirely Knisely's opinion of the role of the liver in water regulation.

erable interest in the vitamin A deficiency seen in cirrhosis Here the bu
de

twenty years for roentgen visualization of the liver The extensive reports on the subject have recently been reviewed by Thomas, Henry and Kaplan These authors reported that in a colloidal suspension of thorium dioxide the particle size varies from 3 to 10 *millimicrons.* A diagnostic dose of 75 cc. of Thorotrast is roughly equivalent to 3 micrograms of radium salt This dose of ionizing radiation is quite capable over the years of producing local necrosis and fibrosis. Although 5 instances of primary hepatic neoplasms have been reported following the injection of Thorotrast, this incidence is considered so low that it precludes thorium dioxide as a carcinogen in man. Of far greater significance is the fibrosis and cicatrization of the liver which occurs as a late complication of the intravenous injection of this material So important did this complication appear to be that it was concluded that this form of hepatosplenography should be used only in instances of extreme urgency or when life expectancy is short

THE LIVER AND NORMAL CONTROL OF BODY FLUID

Closely related to its function as a blood reservoir and as a floodgate between the splanchnic and systemic circulation is the role the hepatic vasculature plays in the volumetric control of body water. As long ago as 1882, Stolnikow pointed out that animals with an Eck fistula rapidly passed into cardiac failure and died when the liver was removed In 1889 Johannson and Tigerstedt wrote, "We see then a considerable quantity of fluid is taken up by the liver and thus withdrawn from the general circulation" In 1894 Bayliss and Starling studied the reaction of various animals to overloads of fluid When water in large amounts was added to the circulation, they found that a considerable proportion of this was taken up by the portal system as evidenced by a great increase in portal pressure compared to that in the vena cava In 1921 Lamson and Roca concluded from their experiments that in the dog the liver accounted for the immediate disappearance from the general circulation of the major portion of intravenously injected isotonic salt solution Their primary evidence for this physiological fact was derived from experiments in which the liver was prevented by an Eck fistula from participating *in this phase of circulatory hemodynamics* In such preparations the rate of disappearance of the salt solution was four times less than in the normal

These investigators proved to their own satisfaction that the site

nerves. In the dog, for instance, the pressure rose promptly from a normal of 8 to 10 mm. of magnesium sulfate solution to as high as 170 to 190 mm. Although these effects were ascribed specifically to splanchnic stimulation, it is entirely possible that they were due to epinephrine. A few years later, François-Franck and Hallion studied the volume responses of the liver to splanchnic stimulation and decided that the diminution in liver volume was due to constriction of the hepatic arterial and portal venous radicles. Burton-Opitz also contributed to this subject by pointing out that the hepatic artery was influenced by nervous stimuli more than was the portal venous system.

Although most of the reported studies have been performed upon dogs, and the consensus was that portal pressure is elevated by splanchnic stimulation, a number of investigators (Schmid, 1909, Hara, 1929, Griffith and Emery, 1930, McMichael, 1932-1933, and Eckhardt, 1935) have studied similar responses in the cat. McMichael, for instance, in 1932 demonstrated that in this animal postganglionic nerves passing into the liver contained vasoconstrictor fibers.

When it was found that splanchnic stimulation produces intrahepatic vasoconstriction, it was natural that students of the subject should desire to see whether vagal stimulation was capable of producing vasodilation. Griffith and Emery (1930) studied this problem extensively and concluded that the vagus nerve does not carry vasodilator fibers. McMichael, two years later, was convinced by his studies that parasympathetic dilator action on the portal or hepatic venules does not exist. This work, done entirely on cats, was in agreement with studies made many years earlier (1914) by Dale.

More recently, observations on the effect of nerve stimulation upon the intrahepatic vessels have been made by Seneviratne. In the rat, tetanizing currents applied to the sympathetic plexus produced a blanching of all of the hepatic sinusoids without affecting the caliber of the portal or hepatic veins. Interestingly enough, this vasoconstrictor effect could be eliminated by ergotamine tartrate. Similar currents applied to the vagus failed to produce a visible effect upon the sinusoids.

The most recent observations on hepatic nervous stimulation are those of Daniel and Prichard. After developing serial roentgenography of the portal venous system to a high degree of accuracy, these investigators demonstrated that severe portal venous constriction follows electrical stimulation of the distal end of the hepatic plexus. In these studies, they employed animals of five different species and reported a similarity of results in all. To the portal venous constriction which was demonstrated they attributed the sharp rise

The ability of the liver to remove or to add fluid selectively to the general circulation has been shown to be under a number of different controls Drugs, toxins, states of shock, and neurogenic mechanisms all participate in exerting their own particular influences over *these mechanisms In resting states, the intermediate phase of filtra*tion can be presumed to be in operation During digestion, when portal blood flow increases tremendously, permeability probably is at its height in order to prevent excesses in water from flooding the general circulation Again it is necessary to emphasize that much of this experimental evidence is derived from animals Although there is reason to believe that comparable reactions take place in man, final proof is not yet available Much more observation and study will have to be devoted to hepatic mechanisms in man before definite conclusions can be reached

NERVOUS CONTROL OF HEPATIC CIRCULATORY ACTIVITY

To give a generally acceptable account of the effects of the nervous system upon the hepatic circulation is a difficult and complex task So many different experiments have been performed upon such a wide variety of animals and under such a host of different conditions that this entire subject is in a state of confusion What can be accepted as the known effects of stimulation of the hepatic nerves upon the circu-

Basch in 1875, it was probably Pal's studies, reported in 1887 and 1888, that established the fact that the liver is under vasomotor control In these early experiments Pal, after excluding all portals of hepatic inflow, was able to show that splanchnic stimulation produced a marked pouring out of blood from this organ He concluded that the splanchnic nerves have a direct effect upon the circulation within the liver Ten years later, Mall repeated a number of Pal's experiments and came to similar conclusions.

The next fifty years of experimental effort in this field were devoted to proving, by indirect means, that stimulation of the hepatic nerves produces intrahepatic vasoconstriction This conclusion was largely deduced from observations upon blood flow, hepatic volume, and changes in venous pressure In 1894 Bayliss and Starling found that the sympathetic nerves supplying the liver arose from the third through the eleventh thoracic segments, with the majority of the fibers coming from the fifth, sixth, seventh, eighth, and ninth segments They also measured the effects of nervous stimulation upon the portal pressure and were able to demonstrate dramatic rises in pressure in the portal vein after stimulation of both splanchnic

all agreed that this hormone produces a marked although transient rise in portal pressure They were unable, however, to confirm A Bauer, Dale and Richards, and Bainbridge and Trevan's observation that the liver increased in volume. In fact quite the opposite was demonstrated, they all noted that the liver shrank in size after an injection of epinephrine This disparity in results received much attention, and many comments were made to prove that the liver responds differently to variations in dosage

It was not until 1932 when H H Bauer and his associates suggested that epinephrine opened a "sphincter mechanism" in the liver that a reasonable explanation for the observed decrease in the size of the liver appeared Here, however, further confusion arose, for emphasis was shifted from a study of the size of the liver to blood flow in and out of this organ Bauer accepted the fact that epinephrine causes a constriction of the branches of the portal venules and hepatic arterioles, but early he emphasized that he was not so much concerned with inflow of blood into the liver as with its outflow through the hepatic veins To study this problem, he and his co-workers employed a perfusion technique which, though carefully controlled, may, as Macgraith has pointed out, have been subject to a serious experimental error At any rate, Bauer and his associates showed that in spite of hepatic arterial and portal venous constriction, there was always an increase in the amount of blood leaving the liver when this organ was subjected to the effects of epinephrine This phenomenon was employed as evidence that in the dog this hormone opened a sphincter mechanism located near the caval openings of the hepatic vein and permitted the liver to dump a large amount of blood into the vena cava It was suspected that failure of caval pressure to rise under these circumstances was due to another action of epinephrine, namely, its ability to increase cardiac output In reporting his experiments, Bauer emphasized the complexities involved in studying the hepatic circulation He wrote, "These actions of the sphincter or sluice mechanism of the dog's liver, together with the chemical and nervous control of the double

[illegible]

could this sphincter or sluice mechanism be demonstrated Although it had been pointed out many times before that there was a marked species difference, Bauer's studies served to focus the physiologist's attention upon the fact that all research upon the hepatic circulation must be delineated most accurately in terms of dosage, drugs used, species of animal studied, and experimental conditions

in portal venous pressure which had been observed so many times to follow splanchnic excitation In addition to these changes in blood pressure and flow, Snyder and Tyler have shown that the flow of hepatic lymph also is mediated by neurovascular responses In all likelihood, this reaction is due to lymph being squeezed out of the liver rather than to any direct action upon the hepatic lymphatics.

REACTION OF THE INTRAHEPATIC VESSELS TO HORMONES, DRUGS, AND TOXINS

Few subjects related to hepatic physiology have been more extensively studied than have the reactions of the intrahepatic blood vessels to a host of hormones, drugs, and toxic agents Nor has any subject suffered more from lack of uniformity in species of animal studied, in experimental methods, and in dosages employed Discrepancies and contradictions in reported results, therefore, are legion In fashioning this review of currently pertinent material, it has been found impossible to consider even briefly all of the innumerable experiments performed in this field Only reports considered of major physiological significance will be included here

Epinephrine

The earliest recorded studies upon the reaction of the portal circulation to epinephrine are those of Oliver and Schafer who in 1894 reported that the spleen shrinks profoundly when subjected to the influence of this hormone In 1905 Bainbridge and Dale studied [illegible]

[illegible] point out that this effect could be obtained only with very large doses Bainbridge continued his interest in this subject, and in 1917 he and Trevan reported that if epinephrine were injected continuously and slowly into the blood stream of a dog, a state of "shock" could be produced This they believed was due to obstruction of blood flow through the liver and sequestration of significant amounts of blood in the abdominal viscera Later the same year these investigators summarized their experiments and concluded that epinephrine produces a marked increase in liver volume and a sharp rise in portal pressure The latter observation had first actually been made many years earlier (1909) by Schmid

During the next ten to fifteen years, numerous physiologists (Edwards, Mautner and Pick, Lampe and Mehes, Baer and Rossler, Burton-Opitz, and Gollwitzer-Meier) studied intensively the effects of epinephrine upon the portal circulation In spite of the numerous different experimental techniques employed, these investigators

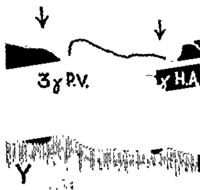
The next important physiological mechanism connected with the hepatic vasculature is that observed by Deysach who in 1941 described his "sluice valve" mechanism. Based upon epinephrine experiments and microscopic sections, Deysach describes this mechanism as follows, "Although it is generally stated that liquid enters the liver lobule by way of the 'portal canals' and that liquid is drained from the liver lobule via the central vein, my own observations show that liquid may also drain directly into the sublobular vein via small endothelial tubes (sluice channels) which arise from the confluence of many ordinary sinusoidal capillaries." Deysach believes many of the conflicting observations made upon the hepatic circulation may be resolved through recognition of this mechanism. Futhermore, these channels offer a pathway by which the blood may be shunted more or less directly through the liver without having to traverse the sinusoids. In stating that this sluice mechanism is opened by epinephrine, Deysach echoes the work of Bauer who noted that in the dog the sphincter is opened by this drug.

At about the same time, Franklin (1937), Katz and Rodbard (1939), and Wakim (1942) reviewed earlier studies regarding the effect of epinephrine upon the hepatic circulation, and each performed a number of additional original experiments. All of these men agreed that the major effect of epinephrine upon the liver is to cause a widespread intrahepatic vasoconstriction and a distinct rise in portal pressure. The reader is referred to these excellent reviews for complete details.

In association with their investigations of portal pressure in hemorrhagic shock, Wiggers and his co-workers in 1946 studied the action of epinephrine on the portal system. They pointed out that small doses of epinephrine are supposed to constrict the mesenteric vessels as well as the portal radicles within the liver. In his experiments, such doses produced a sharp though delayed rise in portal pressure. This delay occurred despite the fact that the spleen during this time emptied itself of considerable quantities of blood. Wiggers attached great importance to this delay, for he believed it meant a marked increase in mesenteric resistance. Furthermore, since portal pressure does not reach its peak until aortic pressure has returned almost to normal, Wiggers also believed that constriction of the hepatic radicles must occur. When Wiggers compared the relationship between mesenteric and hepatic resistance to blood flow, it seemed obvious to him that the initial effect of epinephrine was an increase in mesenteric resistance, while the secondary response was largely a manifestation of a dominant increase in hepatic resistance.

Among the more recent studies upon the effects of epinephrine upon the liver, the most important are those involving the use of

ie following the same dose of epinephrine similarly admin-
In 4 patients with advanced cirrhosis and severe degrees of
hypertension, there was an immediate fall rather than a rise
onse to the same dose of epinephrine (Fig 131 A, B, C, D,
) In all instances, the anticipated rise in systemic arterial



g 49 Dog 57 Macgrath's "blue" preparation If, in preparing the liver erfusion, oxygenation is allowed to lapse even for a short period of time, lue" or abnormal appearing liver is obtained Here adrenaline produces ecrease in hepatic venous outflow (From Macgrath Liver Injury Trans Conference May 21–22, 1951 Josiah Macy Jr Foundation)

ssure appeared A graph of one of the patients in whom epin-
rine produced a fall in portal pressure is reproduced in Fig
50 *

ere, then, is another example of the reversal of the response of
liver to a physiologically active drug, epinephrine In this in
ce, however, this change can only be surmised to be due to the
sis. In seeking a clear explanation for the reversal manifested by

* itional studies upon the effects of epinephrine upon portal pressure in and man are elaborated in Appendix 5

inflow and in the liver volume." Maegraith showed two slides at this meeting demonstrating these differences. The first, Figure 48, shows that epinephrine after injection into either the hepatic artery or portal vein of the "red" liver produces a decreased hepatic output. The second, Figure 49, shows the increase in output produced by a similar injection of epinephrine introduced into the circulation of a "blue" liver. If the "red" liver is allowed to become "blue," there is a reversal of epinephrine effect. Maegraith and his associates interpret this evidence to mean that in the liver there are mechanisms

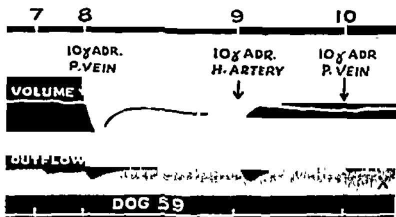


Fig. 48. Dog 59. Maegraith's "red" preparation. During preparation of this liver for perfusion, every precaution is exercised to insure a continuous flow of oxygenated blood. Under these circumstances a "red" liver, healthy in appearance, is obtained. Here adrenaline produces a decrease in hepatic venous outflow. (From Maegraith. Liver Injury. Trans. 10th Conference May 21–22, 1951 Josiah Macy, Jr. Foundation.)

which can alter their reactions to epinephrine. This change these investigators attribute specifically to variations in the oxygenation of the liver. They also suggest that the "red" liver is nearer to the "physiological state" than the "blue."

These observations of Maegraith and of Maegraith, Jones and Andrews were of particular significance to Child, Nestler and Holswade in connection with their studies upon the effect of epinephrine upon the portal pressure of human patients with normal and with cirrhotic livers. In patients with normal livers and a normal portal pressure, the injection of 0.5 cc. of 1:1000 epinephrine into a small

fatty degeneration) and mild portal hypertension, the portal pressure

also rose following the same dose of epinephrine similarly administered In 4 patients with advanced cirrhosis and severe degrees of portal hypertension, there was an immediate *fall rather than a rise* in response to the same dose of epinephrine (Fig 131 A, B, C, D, p 349) In all instances, the anticipated rise in systemic arterial

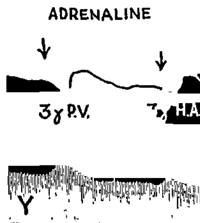


Fig 49 *Dog 57 Macgraith's "blue" preparation If, in preparing the liver* for perfusion, oxygenation is allowed to lapse even for a short period of time, a "blue" or abnormal appearing liver is obtained Here adrenaline produces an increase in hepatic venous outflow (From Macgraith Liver Injury Trans 10th Conference May 21–22, 1951 Josiah Macy, Jr Foundation)

pressure appeared A graph of one of the patients in whom epinephrine produced a fall in portal pressure is reproduced in Figure 50 *

Here, then, is another example of the reversal of the response of the liver to a physiologically active drug, epinephrine In this instance, however, this change can only be surmised to be due to the cirrhosis In seeking a clear explanation for the reversal manifested by

* Additional studies upon the effects of epinephrine upon portal pressure in dog, monkey, and man are elaborated in Appendix 5

the patient with portal hypertension due to cirrhosis, an experiment performed by McMichael many years ago appears to be relevant. In 1932 this investigator became interested in the then poorly understood condition termed "splenic anemia," or Banti's disease. It was M[illegible]'s hypothesis that the hemorrhages in the spleen and the t[illegible] were anatomical expressions of [illegible] McMichael believed that the [illegible] physiology," he set abou[illegible]

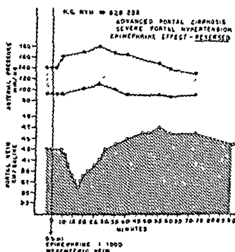


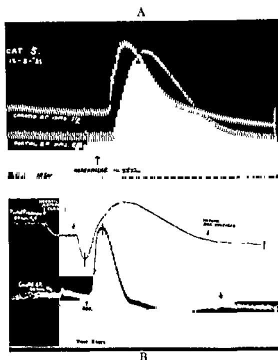
Fig. 50. Graph of the effect of epinephrine upon portal pressure in a patient with severe portal hypertension due to advanced cirrhosis. (See Appendix 5, Figures 124–131.)

ephrine upon this unique circulatory system. As a result of his studies, which were performed upon normal cats, McMichael confirmed the increases in portal pressure and decreases in liver volume which had been shown so many times before to follow an injection of epinephrine. He deduced from his experiments that this hormone "first causes a vasoconstriction of the ramifications of the portal vein in the liver leading to a rise in portal pressure, a secondary rise occurs from an increased flow of blood in the portal system through the hepatic and mesenteric arteries." In Figure 51 A is reproduced one of McMichael's typical epinephrine curves. It demonstrates particularly well the primary and secondary rises in portal pre[illegible]e which are encountered in the cat.

The experiment of McMichael which interested Child and his associates, particularly in connection with their demonstrated reversal of the epinephrine curve in patients with adva[illegible]ed cirrhosis

and portal hypertension, is described by McMichael as follows, "If the portal vein is occluded partially by means of a ligature applied near the hilus of the liver, the portal outflow is so obstructed that the pressure sets itself at a higher level, and alterations in pressure in the

A



B

Fig 51 A Typical adrenaline effect upon the portal pressure of the cat The same sharp rise is also seen in the dog

B In this interesting experiment McMichael partially obstructed the portal vein and totally occluded the hepatic artery Injection of adrenaline then produced a fall rather than a rise in portal venous pressure The similarity between this experiment, the "red" and "blue" preparations of Macgraith, and Child's cirrhotic livers is striking As yet a wholly satisfactory explanation of these phenomena has not been found (From McMichael J Physiol, vol 75, 1932)

portal vein dependent on intrahepatic effects of adrenalin are prevented from manifesting themselves on the portal pressure record By clamping the hepatic artery and thus preventing adrenalin from reaching the liver, the intrahepatic effects can also be abolished Under these circumstances the injection of adrenalin is followed by an immediate fall in portal pressure, which begins as soon as the arterial pressure starts to rise The moment that the arterial pressure

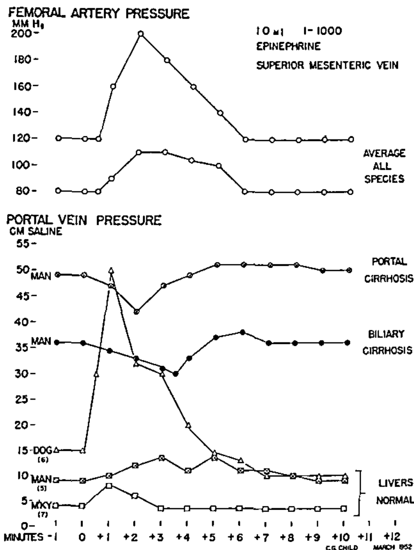


Fig 52. Comparison of effects of 1.0 ml. of 1 1000 epinephrine injected into a small branch of the superior mesenteric vein in man, monkey, and dog. In the patients with cirrhosis in whom the epinephrine effect was reversed, the cirrhosis was far advanced Similar studies in patients with minimal cirrhosis, yet manifesting comparable degrees of portal hypertension, failed to manifest a reversal effect, their curves followed that seen in normal man.

passes its summit, however, the portal pressure begins to rise again and reaches its highest about the time that the arterial pressure returns to normal" McMichael's original graph is reproduced in Figure 51 B. In Figure 52 are summarized our experiments in the dog, monkey, and man (normal liver and cirrhotic liver) after the injection of epinephrine into the portal circulation

To attempt to explain why an abnormal liver responds abnormally to at least one form of stimulation, namely, epinephrine, has been a great temptation As evidence accrues concerning vascular abnormalities in the cirrhotic liver, a number of mechanisms present themselves upon which to base an hypothesis Certainly the cirrhotic liver

possibility might relate significantly to the intrahepatic vessels; perhaps these are so changed by the cirrhotic process that they are unable to respond to epinephrine Yet another conjecture involves the abnormal connections between the hepatic artery and portal venous and hepatic venous elements which are known to appear in

hormone At the moment, the only logical conclusion warranted concerning this unusual phenomenon is that it has not been studied extensively enough to justify any explanation at all

Pituitary Extract

As soon as the response of the hepatic circulation to epinephrine was (biologically produced and he studied Oliver in 1897 of a pituitary extract upon small veins He noticed that in the frog the mesenteric vein contracted under the influence of pituitary extract Gollwitzer-Meier and McMichael have studied the effect of this hormone, and both demonstrated that it produces a fall in portal pressure Clark, Wiggers, Charkravarti and Tripod, and Katz and Rodbard have studied the action of pitressin upon the liver and substantiated the general observation that the portal pressure decreases under the influence of this hormone The changes in arterial pressure have usually been an initial rise followed by a fall Both of these effects are prolonged and do not manifest the prompt recovery seen after the use of epinephrine The generally accepted explanation for this fall in portal venous pressure lies in the ability of vasopressin to constrict the

splanchnic capillaries and arterioles, thereby excluding blood from the portal system. This concept has been confirmed by Wiggers.

Histamine

The remarkable swelling of the liver produced by histamine was first noticed by Mautner and Pick in 1915 Baer and Rossler, a few years later, demonstrated a sharp increase in portal pressure concomitant with the increase in liver volume Bauer, Dale, and their associates made an exhaustive study of the reaction to histamine and in 1932 reported the characteristic effects upon the portal circulation: a marked increase in liver volume associated with a comparable increase in portal pressure These observations led these investigators to propose their theory of an hepatic sphincter in the dog's liver They pointed out that the hepatic veins in this animal contain so much smooth muscle that their vigorous contraction can impound large amounts of blood at greatly increased pressure within the portal bed This large amount of smooth muscle had been noted by Arey and Simonds Elias and Feller had been able to show comparable amounts of smooth muscle in the hepatic veins in man While the presence of large bands of smooth muscle could be demonstrated in the dog and in man, they could not be found in the cat and the goat This was consistent with Bauer and Dale's observation that in these two animals increase in liver volume and portal pressure did not appear after the injection of histamine. Katz and Rodbard (1939) also studied the action of histamine and confirmed the earlier findings They ascribed the phenomena to the direct action of histamine upon the hepatic sphincter. Seneviratne also studied the liver directly after the administration of histamine. He observed a marked dilatation of the sinusoids which he believed could be due either to an obstructed outflow or to a retarded inflow at reduced pressures. He finally expressed the opinion, however, that this drug reacts directly upon the sinusoidal wall producing a widespread dilatation. That histamine causes a liver volume and portal pressure increase in dogs and in monkeys has been amply confirmed in our laboratory Because the use of this drug during surgical operation has been considered excessively hazardous, its action in man has not been studied.

Wiggers (1946) accepted with reservation the concept that histamine constricts the venous sphincters at the caval ends of the hepatic veins Although his curves after histamine administration show a marked increase in portal pressure, he suggests that this might well be due to dilatation of the mesenteric vessels As the effects of this drug continue, Wiggers finds it difficult to avoid the conclusion that the responses are due to marked increase in resistance to hepatic

outflow. He, too, then agrees to the popularly held concept that histamine produces marked obstruction to hepatic outflow.

Acetylcholine (Hunt, Snyder; Bauer, Dale, Poulsson and Richards; Katz and Rodbard)

Acetylcholine has been considered to have some important action even though the liver reacts but slightly if at all to vagus stimulation Bauer and his associates failed to notice any appreciable effect, while Katz and Rodbard demonstrated that large doses produced a fall in portal and arterial pressure together with a decrease in portal flow Snyder has described the effects of acetyl-beta-methylcholine as producing a short period of increased inflow which he suggests may be due to dilatation of the sinusoids and a simultaneous increase in rate of outflow These brief effects are followed by a sharp decrease in outflow and inflow associated with a sharp increase in inflow of hepatic lymph Snyder suspects that this bloc occurs in the hepatic venous rather than in the portal system Wakim *(1944)* saw no effect from small doses, while large doses, coincidentally with slowing of the heart rate, seemed to produce a decrease in rate of flow through the sinusoids and some engorgement of these structures So rapid was the recovery that Wakim intimates that the hepatic reactions were largely secondary to the cardiac effects Seneviratne, also employing the direct observation technique, failed to observe an important intrahepatic effect due to acetylcholine

Thyroxin

Wakim administered thyroxin to cats daily over a ten-day period From the second day on, there was evidence of marked increase in intrahepatic circulatory activity No longer did the liver manifest its *normal rhythm, and arteriovenous communications,* which normally are visible only occasionally, were readily identified in large numbers After withdrawing the thyroxin, the liver slowly returned to normal over about a ten-day period This observation, of course, is of some interest, for a relationship between the liver and the thyroid has long been suspected though its nature has not been known Precisely of what importance this apparent increase in circulation is cannot yet be clearly defined

Bile Acids

In 1941 Grodins, Osborne, Ivy and Goldman were able to show that any hydrocholeretic such as sodium hydrochlorate or cinchophen increased the blood flow in the hepatic artery They also showed that this increase in arterial flow was not essential for a choleretic response to bile salts

Nor-Epinephrine

This recently isolated hormone has been extensively studied by West and by M Mann and West These investigators found that stimulation of the hepatic and splenic nerves produced nor-epinephrine in amounts sufficient to cause an elevation in portal pressure comparable to an intraportal injection of this same material. In connection with this hormone, Child has noticed, as have others, that when it is injected into the femoral vein, the systemic arterial pressure rises about 30 per cent When, however, a comparable dose is injected into the portal vein, arterial pressure is elevated only 11 per cent The implication, of course, is that this hormone is partially destroyed in the liver

MISCELLANEOUS OBSERVATIONS ON THE INTRAHEPATIC CIRCULATION

In addition to the major observations made upon the physiology of the hepatic vasculature, there are a few others which seem to merit brief note

Hypertonic Solutions

Seneviratne observed that when either 30 per cent solutions of sodium chloride, 50 per cent solutions of urea, or 50 per cent glucose solutions were injected, the effects upon the liver were all comparable When given intraportally, the sinusoids immediately contracted, then relaxed slowly entering a phase of dilatation within a variable period of time—fifteen minutes for the sugar solution, much longer in the case of urea

Respiration

Many of the older physiologists were greatly interested in the slight

also McMichael believed this phenomenon to be caused by changes in intra-abdominal pressure, but since it also appears when the abdomen is widely opened, this cannot be the major factor. The consensus seems to be that these minor and rhythmic variations in pressure are indirectly due to respiration, when the diaphragm contracts, it squeezes the liver gently and sufficiently to impede fleetingly the exit of the blood through the hepatic veins Seneviratne showed that when respirations became deep and labored, the liver paled and the sinusoids contracted slightly When respiratory obstruction was released, the sinusoidal flow returned promptly to normal

Seneviratne also investigated the effect of anoxia upon the sinusoids In this state they dilated widely and the animal died Under states of hypoxia, sinusoidal dilatation progressed slowly reaching its maximum after about an hour At this time, blood flow was very slow, and in some sinusoids stasis was complete In this stage the reaction

[illegible]

able to recover completely

Trauma, Heat, and Cold to Body Surface, and Hemorrhage

Seneviratne studied the effect upon sinusoidal flow of a number of stimuli which any organism may encounter in the course of its day-to-day existence Trauma in the form of a severe crushing injury to an extremity produced an immediate constriction of all the sinusoids After ten to fifteen minutes, the contraction passed into a state of wide dilatation The sinusoids were packed with red cells, and hepatic circulation appeared greatly retarded In these experiments, performed upon rats, many of the animals died in from one to two hours Heat applied to the body surface produced immediate contraction followed by dilatation lasting as long as the stimulus was continued Cold also caused an immediate sinusoidal contraction which, however, was not followed by dilatation Heat and cold applied to the liver directly produced similar effects, that is, initial contraction and dilatation following heat and a prolonged contraction following cold The response to hemorrhage was dramatic, the entire liver paled and the sinusoids contracted so tightly as to disappear from view This mechanism reflects the blood reservoir function of the liver, in blood loss the splanchnic and hepatic circuits are effectively removed from the circulation, thereby maintaining as long as possible the flow of blood to more essential organs

Selective Distribution of Portal Blood to the Liver

Although different experimental methods were used by these investigators, Sérégé, Bartlett and his associates, Copher and Dick, and others have all demonstrated conclusively a so-called "streamlined effect" in the distribution of portal blood to the liver Basically this effect was discovered by the injection of dyes and particulate matter into various areas of the portal bed It was shown that blood from the right half of the portal bed finds its way to the right half of the liver, while that from the left half of the portal bed flows primarily to the left lobe of the liver For some time investigators were attracted to the idea that this partitioning of the portal blood within the liver

pointed to a different function of the cells in various areas of the liver This hypothesis could never be proved, and Senevıratne, though he too observed the "streamlined effect," also noticed that within a relatively short time the mixing of blood throughout the liver was so extensive that eventually all substances of splanchnic origin found their way to all parts of the liver.

CHAPTER 8

The Intrahepatic Vascular Changes in Liver Disease

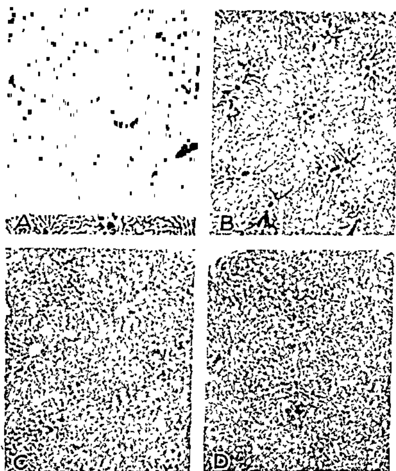
GENERAL consideration of the effects of injury upon a composite organ such as the liver reveals that these may be conveniently considered under two headings—*immediate* and *delayed*. The injury may be so overwhelming as to lead to massive hepatic necrosis and immediate death of the organism within a few hours to days. On the other hand, the response to the insult may be so subtle and insidious that its effects cannot be detected for many months or [illegible]

[illegible] remain only the cells of the vascular system, the fibrous tissue in the portal tracts, and the components of the reticular endothelial system. These seem to be the last to suffer damage.

ACUTE LIVER DAMAGE

In acute hepatic lesions, whether the cause be infectious or chemical, the damage to the parenchymal cell is most conspicuous. For instance, within a few hours after exposure to carbon tetrachloride or chloroform, the liver cells become pale and swollen (Cameron and Karunaratne). This parenchymatous swelling produces narrowing of the sinusoids sufficient in degree to occlude completely sinusoidal blood flow. This is clearly demonstrated in Figure 53, where the effects of cellular edema prevent India ink injected into the portal vein from penetrating to the central vein. Before the significance of this particular reaction was clearly understood, the reason for the appearance of necrosis at the center of the lobule rather than at its periphery proved to be one of the most perplexing observations in experimental pathology. Why did carbon tetrachloride not kill the cells near the periphery of the lobule which surely absorbed it in greater concentration? The diffuse swelling of all lobular paren-

chymatous cells, producing as it does diminished blood flow through the sinusoids, effectively prevents blood from reaching the center of the lobule Central lobular necrosis, then, is perhaps a manifestation of ischemia rather than of parenchymatous intoxication That this



sinusoids are imp[illegible] upon [illegible]
the lobule (After Himsworth)

concept can be applied to hepatic disease in man is borne out by the study of the lesions produced by infectious hepatitis In this disease, Lucké has shown a central lobular necrosis which closely simulates that seen in the experimental animal following exposure to carbon tetrachloride. The reason for the survival of the cells in the periph-

ery of the lobule in both instances is believed to be the fact that these cells are near enough the source of blood flow (portal tracts) to assure them a sufficient quantity of blood to maintain cellular viability

In all experiments comparable to those in which minimal doses of various toxic agents are employed, it is obvious that hepatic cells can be damaged selectively both in regard to location and to total numbers It seems equally clear that a sinusoidal decrease in blood flow plays a definitive role in causing injury to the cells In none of the reported studies is it indicated that blood vessel injury in itself is important The volume and rate of blood flow, as reflected in physiological variations and pathological abnormalities, must be considered at least one important factor in hepatic disease, the extent and limitations of which have not as yet been clearly defined

Toxic substances can naturally be administered in such large amounts that complete necrosis of all hepatic components appears In similar fashion, various acute catastrophes may overtake the liver, such as occlusion of both the hepatic artery and portal vein or the appearance of acute yellow atrophy, which result in massive necrosis and total liver failure Of subtler import in relation to liver disease is the concept that a single, relatively severe insult or oft repeated minor insults may lead to the establishment of a chronic process within the liver which may then perpetuate itself The various cirrhoses of the liver conform to such an hypothesis and fulfill the criteria of what may broadly be termed chronic injury to the liver Here again the blood vessels and their complex relationships play an important subsidiary if not a dominant primary role

CHRONIC LIVER DAMAGE PORTAL CIRRHOSIS

Although John Brown (1685), Matthew Baillie (1797) and Laennec (1826) firmly established cirrhosis of the liver as a pathological entity, they were concerned primarily with the gross appearance of the organ, its size, its consistency, and its color Very shortly after their original descriptions, a number of observations were made indicating that not only were the liver cells and the interstitial connective tissue involved in this morbid process, but also the hepatic circulatory components were implicated The first comprehensive account of the changes taking place in the vascular structures of the liver is perhaps that of Frerichs Writing in 1861 on cirrhosis of the liver under the heading of *Chronic Atrophy of the Liver*, Frerichs states, Important alterations may be distinguished in the blood vessels, the portal vein is usually considerably enlarged as far as its subdivisions into capillaries The walls of the enlarged veins are sometimes normal but at other times they present a remarkable

thickening This thickening disappears suddenly where the capillary ramifications commence The capillaries themselves are in a great measure destroyed hence injections of the portal vein usually succeed very imperfectly It is only here and there that a few isolated capillaries become filled as far as their anastomoses with the roots of the hepatic veins, the latter are more easily injected and the injection runs to a greater distance The meshes formed by the capillary vessels are contracted, and at some places completely disappear The hepatic veins may in many cases participate in the enlargement of the vena porta . . The hepatic artery has appeared somewhat smaller than natural . "

These observations upon the hepatic vasculature made by Frerichs over one hundred years ago have stimulated the interest at one time or another of all investigators of hepatic disease In 1882–83 Sabourin demonstrated clearly that in cirrhosis an intrahepatic collateral circulation forms between the hepatic arterioles and the portal vein. In 1905 the renowned pathologist Richard Kretz expended considerable effort in clarifying the relationship of cirrhosis to the hepatic vasculature He pointed out that in the cirrhotic liver a minute area of parenchyma perhaps the size of a pea may contain from one to five central veins Furthermore, in many of the small islets of parenchyma which remain in the cirrhotic liver the central veins are eccentrically placed It is important that Kretz concluded that this eccentric position could only have been caused by asymmetrical degeneration and regeneration of liver cells In addition, Kretz described many areas of parenchymal tissue devoid of central veins.

Extending his studies to injected preparations of cirrhotic livers, Kretz noted and emphasized the fact that when the portal vein was injected, the celloidin used frequently passed directly into the

of portal blood traversed the sinusoids in its passage into the hepatic veins; and second, that an excess of hepatic arterial blood probably found its way into the portal system Both the "lengthening and narrowing of the capillary vessels and the excess of arterial blood," Kretz believed to be the "true causes of the increase in portal pressure as is shown by the occurrence of ascites in subacute atrophy of the liver with regeneration " Kretz's assistant, Dr. Helly, also compared specimens of normal and cirrhotic livers injected through the hepatic and portal veins For the first time these men demonstrated the marked restriction of the two venous beds in cirrhosis To as great a degree as anyone, Kretz, then, is responsible for focusing at-

tention on the abnormalities in hepatic vasculature which play an important role in portal cirrhosis

About two years later, Herrick (1907) approached the problem of circulatory changes in cirrhosis in a more dynamic fashion Instead of drawing deductions from microscopic sections and injected preparations, he undertook the evaluation of intrahepatic pressure dynamics by perfusing normal and cirrhotic livers removed at autopsy When he perfused the cirrhotic liver through the hepatic artery, Herrick believed he could demonstrate that more fluid passed out through the portal vein in the cirrhotic than in the normal liver Upon this observation Herrick based his theory that, as the cirrhotic process progressed, abnormal communications developed between the hepatic artery and the portal venous system He concluded that this accounted for the rise in portal pressure in cirrhosis Herrick claimed that the effects of this abnormal arteriovenous shunting were clearly reflected in the fact that portal pressure rose 1 mm of mercury for every 6 mm. elevation in hepatic arterial pressure, in a normal liver it required 40 mm of mercury elevation in hepatic arterial pressure to raise the portal pressure a similar (1 mm) amount

Twenty years after Herrick's original approach to the physiology of hepatic circulation, McIndoe undertook similar investigations By combining his observations with both perfusion and infusion techniques, he succeeded in producing a classic article upon the circulatory abnormalities in the liver induced by the cirrhotic process

cirrhotic with
by the marked
showed that the

main portal and hepatic links were distorted and stenosed and the tiny venules twisted In the normal liver these structures are robust, while in the abnormal they are shriveled The bizarre configuration of the hepatic vascular trees in cirrhosis McIndoe beautifully demonstrated by his injection technique He clearly showed that in the cirrhotic liver, the portal veins are curled upon themselves and

the hepatic artery. The hepatic veins and portal venules shared equally in the most pronounced changes Although in a number of instances the hepatic artery was enlarged, this enlargement was not as consistent as Kretz had believed, for this vessel was not infrequently atrophic and smaller than normal

In the cirrhotic liver, McIndoe was unable to find evidence of

thickening . . . This thickening disappears suddenly where the capillary ramifications commence. The capillaries themselves are in a great measure destroyed . . . hence injections of the portal vein usually succeed very imperfectly. It is only here and there that a few isolated capillaries become filled as far as their anastomoses with the roots of the hepatic veins, the latter are more easily injected and the injection runs to a greater distance. The meshes formed by the capillary vessels . . . are contracted, and at some places completely disappear. The hepatic veins may in many cases participate in the enlargement of the vena porta . . . The hepatic artery has appeared somewhat smaller than natural . . ."

These observations upon the hepatic vasculature made by Frerichs over one hundred years ago have stimulated the interest at one time or another of all investigators of hepatic disease. In 1882–83 Sabourin demonstrated clearly that in cirrhosis an intrahepatic collateral circulation forms between the hepatic arterioles and the portal vein. In 1905 the renowned pathologist Richard Kretz expended considerable effort in clarifying the relationship of cirrhosis to the hepatic vasculature. He pointed out that in the cirrhotic liver a minute area of parenchyma perhaps the size of a pea may contain from one to five central veins. Furthermore, in many of the small islets of parenchyma which remain in the cirrhotic liver the central veins are eccentrically placed. It is important that Kretz concluded that this eccentric position could only have been caused by asymmetrical degeneration and regeneration of liver cells. In addition, Kretz described many areas of parenchymal tissue devoid of central veins.

Extending his studies to injected preparations of cirrhotic livers, Kretz noted and emphasized the fact that when the portal vein was injected, the celloidin used frequently passed directly into the hepatic veins, leaving large areas of the parenchyma uninjected. In summarizing his studies on the cirrhotic liver, Kretz apparently conceived of two important abnormalities: first, that only a small part of portal blood traversed the sinusoids in its passage into the hepatic veins, and second, that an excess of hepatic arterial blood probably found its way into the portal system. Both the "lengthening and narrowing of the capillary vessels and the excess of arterial blood," Kretz believed to be the "true causes of the increase in portal pressure as is shown by the occurrence of ascites in subacute atrophy of the liver with regeneration." Kretz's assistant, Dr. Helly, also compared specimens of normal and cirrhotic livers injected through the hepatic and portal veins. For the first time these men demonstrated the marked restriction of the two venous beds in cirrhosis. To as great a degree as anyone, Kretz, then, is responsible for focusing at-

tention on the abnormalities in hepatic vasculature which play an important role in portal cirrhosis

About two years later, Herrick (1907) approached the problem of circulatory changes in cirrhosis in a more dynamic fashion Instead of drawing deductions from microscopic sections and injected preparations, he undertook the evaluation of intrahepatic pressure dynamics by perfusing normal and cirrhotic livers removed at autopsy When he perfused the cirrhotic liver through the hepatic artery, Herrick believed he could demonstrate that more fluid passed out through the portal vein in the cirrhotic than in the normal liver Upon this observation Herrick based his theory that, as the cirrhotic process progressed, abnormal communications developed between the hepatic artery and the portal venous system. He concluded that this accounted for the rise in portal pressure in cirrhosis Herrick claimed that the effects of this abnormal arteriovenous shunting were clearly reflected in the fact that portal pressure rose 1 mm of mercury for every 6 mm elevation in hepatic arterial pressure, in a normal liver it required 40 mm of mercury elevation in hepatic arterial pressure to raise the portal pressure a similar (1 mm) amount

Twenty years after Herrick's original approach to the physiology of hepatic circulation, McIndoe undertook similar investigations By combining his observations with both perfusion and infusion techniques, he succeeded in producing a classic article upon the circulatory abnormalities in the liver induced by the cirrhotic process Comparing the hepatic circulatory systems of the cirrhotic with those of the normal liver, McIndoe was first struck by the marked *diminution in the size of* the total vascular bed He showed that the main portal and hepatic links were distorted and stenosed and the tiny venules twisted In the normal liver these structures are robust, while in the abnormal they are shriveled The bizarre configuration of the hepatic vascular trees in cirrhosis McIndoe beautifully demonstrated by his injection technique He clearly showed that in the cirrhotic liver, the portal veins are curled upon themselves and twisted beyond recognition In advanced phases of this disease, they finally are broken up into a greatly diminished network of stunted vessels These same changes to a lesser degree were demonstrated in the hepatic artery The hepatic veins and portal venules shared equally in the most pronounced changes Although in a number of instances the hepatic artery was enlarged, this enlargement was not as consistent as Kretz had believed, for this vessel was not infrequently atrophic and smaller than normal

In the cirrhotic liver, McIndoe was unable to find evidence of

orderly interposition of sinusoids between the portal and hepatic venous trees, these did not alternate nicely but frequently lay close together leaving great gaps and free spaces, obviously the sites of regenerating nodules of liver cells. He deduced from his injection techniques that these areas of new parenchyma were devoid of

hepatogram in which the dye is evenly distributed throughout the liver. In animals with cirrhosis induced by butter yellow, the hepatograms showed innumerable rounded areas of abnormal radiolucency indicating that the nodules of regenerated liver cells were devoid of blood vessels As a result of areas of regeneration of liver parenchyma, the central veins were pushed to the periphery McIndoe concluded that as the cirrhotic process progressed, slowly the vessels in the liver tended to disappear First the veins succumbed, then the arterial components. He did not believe that this was caused by a progressive pseudophlebitic process but merely by pressure Actually, McIndoe felt that the process was quite comparable to pressure atrophy as seen elsewhere in the body but that the effects were disastrous in so far as liver function was concerned The hepatic cells became buried in a mantle of scar tissue and effectively separated from their blood supply Parenchymal nutrition was consequently severely compromised For a period after the veins have disappeared, the liver is supported entirely by arterial blood When this finally fails, hepatic death occurs

Although McIndoe could not validate Herrick's observations in regard to arteriovenous communications, he performed a series of perfusion experiments which he considered most significant. In the normal liver, he was able to collect from the hepatic vein 100 per cent of the perfusate injected into the portal vein. In the cirrhotic liver, however, only 13 per cent could be so retrieved When he injected the hepatic artery, the perfusate returned both by the portal and hepatic veins as well as through collaterals. On the basis of these experiments, McIndoe became convinced that the obstruction to portal flow resulted in portal hypertension, and in 1928 he suggested that an Eck fistula be tried for the relief of this condition rather than, as Eck had suggested, to relieve ascites. McIndoe's suggestion, however, went unheeded for another ten to fifteen years

In 1942 Dock attempted to repeat these experiments of Herrick and McIndoe. He obtained different results in alcoholic and non-alcoholic cirrhotic livers and showed an increase in arterial perfusibility in the alcoholic cirrhotic which he was not able to demonstrate in the non-alcoholic. As a result of his studies, he postu-

lated a reciprocal relationship between the hepatic artery and the portal venous flow proportional to the degree of arterial pressure and of intrahepatic resistance

Although hardly a vascular component, the fibrous tissue developing in cirrhosis plays such an important role in compromising blood flow through the hepatic vessels that its origin merits special consideration Original observers such as Brown, Baillie, Laennec, Carswell, Charcot, and Frerichs regarded cirrhosis primarily as an inflammatory and sclerosing hyperplasia of supporting connective tissue This view was supplanted at the turn of the century by a more realistic conjecture, namely, that the fibrosis was a response to parenchymal degeneration More recent thinking assumes that the proliferation of connective tissue is a reparative process stimulated by hepatic cellular necrosis From time to time, other theories have been developed such as that of Rossle who believed that cirrhosis was a serous inflammatory process associated with increased capillary permeability His theory has never received very enthusiastic support A further elaboration in the interpretation of fibrosis comes from the experiments reported by Himsworth who demonstrated that viable liver transplants evoke a marked fibroplasia, while those which have been boiled do not Himsworth believed that this was evidence of a specific ability of viable liver tissue to provoke fibroplasia.

In the normal as well as in the cirrhotic liver, the fibrous connective tissue presents a septal-like distribution Furthermore, in the normal liver this tissue occurs only in the portal tracts For these two reasons, the excessive amount of fibrous tissue which characterizes cirrhosis was for many years believed to originate solely from the portal tracts This assumption undoubtedly accounted for the compounding of "portal" and "cirrhosis" to produce the term which even today is widely applied to the most commonly encountered form of chronic liver damage Recently evidence has appeared indicating that much of the fibrous tissue readily observed in a cirrhotic liver does not originate in the portal tracts but actually arises around the central vein This concept is based on the studies of Ashburn, Endicott, Daft and Lillie who, in 1947, produced dietary cirrhosis in rats and carbon tetrachloride cirrhosis in guinea pigs In the heavy connective tissue trabeculae seen in these two forms of experimental cirrhosis, the vessels could not be filled with an injection mass introduced into the portal vein Only when it was introduced into the hepatic veins could the small vessels in these newly formed fibrous-tissue trabeculae be filled with the injection mass Here was a new aspect that cast serious doubt on the older hypothesis that the connective tissue appearing in cirrhosis derives from the portal tracts

orderly interposition of sinusoids between the portal and hepatic venous trees; these did not alternate nicely but frequently lay close together leaving great gaps and free spaces, obviously the sites of regenerating nodules of liver cells He deduced from his injection techniques that these areas of new parenchyma were devoid of vessels Recently, this original observation has been beautifully substantiated by Steinberg and Martin who showed roentgenographically that in the normal rat's liver thorium dioxide gives a diffuse

indicating that the nodules of regenerated liver cells were devoid of blood vessels As a result of areas of regeneration of liver parenchyma, the central veins were pushed to the periphery McIndoe concluded that as the cirrhotic process progressed, slowly the vessels in the liver tended to disappear First the veins succumbed, then the arterial components He did not believe that this was caused by a progressive pseudophlebitic process but merely by pressure. Actually, McIndoe felt that the process was quite comparable to pressure atrophy as seen elsewhere in the body but that the effects were disastrous in so far as liver function was concerned The hepatic cells became buried in a mantle of scar tissue and effectively separated from their blood supply Parenchymal nutrition was consequently severely compromised For a period after the veins have disappeared, the liver is supported entirely by arterial blood When this finally fails, hepatic death occurs

Although McIndoe could not validate Herrick's observations in regard to arteriovenous communications, he performed a series of perfusion experiments which he considered most significant. In the normal liver, he was able to collect from the hepatic vein 100 per cent of the perfusate injected into the portal vein. In the cirrhotic liver, however, only 13 per cent could be so retrieved. When he injected the hepatic artery, the perfusate returned both by the portal and hepatic veins as well as through collaterals. On the basis of these experiments, McIndoe became convinced that the obstruction to portal flow resulted in portal hypertension, and in 1928 he suggested that an Eck fistula be tried for the relief of this condition rather than, as Eck had suggested, to relieve ascites. McIndoe's suggestion, however, went unheeded for another ten to fifteen years

In 1942 Dock attempted to repeat these experiments of Herrick and McIndoe He obtained different results in alcoholic and non-alcoholic cirrhotic livers and showed an increase in arterial perfusibility in the alcoholic cirrhotic which he was not able to demonstrate in the non-alcoholic. As a result of his studies, he postu-

their total number reduced The portal branches were arranged in basket-like fashion about the cirrhotic nodules, and the hepatic veins were flattened and distorted Popper also observed that the portal and hepatic veins were generally thin-walled and appeared free of signs of inflammatory reaction Furthermore, it was quite evident that the fibrosis extended from the portal triads to the central field and involved the branches of the hepatic veins

Elias believes that his findings confirm Ashburn's observations that the fibrous septa, in the experimental animal at least, originate from the central fields, because in the early stages of induced cirrhosis they can be injected only through the hepatic veins. At first glance, this might mean that experimental and human cirrhosis were essentially different processes But, say these observers, a difference in stage could easily account for the variations seen. Although the single steps cannot as yet be traced, it appears characteristic of Laennec's cirrhosis that in its fully developed state the fibrous septa contain vessels connected directly with both the portal and hepatic veins Such connections, of course, cannot be demonstrated in the normal liver These interrelationships are clearly shown in one of these authors' illustrations which is reproduced in Figure 54 Elias gives credit to the older investigators such as Kretz, McIndoe, and Herrick for suspecting the presence of these extensive anastomoses which seem to carry off a considerable amount of blood before it even approaches the parenchymal cells In effect, then, these act as an Eck fistula in so far as hepatic cellular nutrition is concerned Of particular interest in the studies is the observation that most of these abnormal anastomoses are remnants of previous sinusoids that have dilated and the walls of which have become thickened The remaining sinusoids are presumed to disappear It is interesting to question whether or not the sinusoids that persist may not be the shunts Deysach referred to previously

Commenting upon the distortion of the venous trees, Elias points out particularly that the flattening of the small venules may well be due to regenerating liver nodules as demonstrated by Kelty, Bag-
s, is
pos-
[illegible] In
conclusion, Elias expressed the belief that development of multiple intrahepatic venovenous and arteriovenous shunts which work to the distinct detriment of the liver cell is a process "common to and significant in the pathogenesis of all types of cirrhosis"

The intrahepatic circulatory dynamics in experimental cirrhosis have recently been extensively studied by Daniel, Prichard and Reynell These investigators produced carbon tetrachloride cirrhosis in

It certainly indicates that at least a portion of the fibrosis in cirrhosis of the liver arises about the central veins. If this be true, it would account for many of the older observations on the cirrhotic liver

could be demonstrated with fat stains Fat cysts could be easily outlined in animals sacrificed early in the course of their disease In other rats sacrificed at definite intervals, these cysts coalesced into larger and larger droplets and were replaced by scar tissue around the central vein In animals followed long enough, the connective tissue masses eventually involved the portal area as well.

Another aspect of the theory that the fibrous tissue in cirrhosis stems from the portal tracts is found in a consideration of the small bile ducts which can invariably be demonstrated within the stroma of this new tissue. These little canaliculi, it was reasoned, could only have come from the bile ducts of the portal tracts Those supporting the theory of central origin of cirrhotic fibrosis maintain that this reason for believing that these bile ducts originate in the portal tracts *is not necessarily valid These investigators believe that often in* degeneration of the parenchymal cell there is such a profuse regen-

These controversial studies stimulated Elias and his associates, already noted for their important observations upon the structure of the normal liver, to investigate the cirrhotic liver. Their recent article must be considered an important contribution to the large

livers The preparations were then studied by means of thick and thin microscopic sections In the fibrous septa of the rats' livers injected via the hepatic veins, numerous tortuous vessels were found

injection through either the portal vein or the hepatic vein Many communications between the portal and hepatic veins could be seen When injected by way of the hepatic artery, the specimens showed many connections between the arterial and venous systems. In all the specimens these investigators confirmed McIndoe's observations. that the vascular trees were all tortuous, irregular, and

even in this type of cirrhosis, abnormal communications develop between the portal and hepatic venous system In Figure 55 A and B are reproduced two of Daniel's hepatograms, one of the normal liver and one of the cirrhotic



Fig 55 Thorotrast hepatogram in the rat A A normal liver, B a cirrhotic liver. In the normal liver (A) there is diffuse filling of the entire liver, while in B the distortion of the portal venous tree is evident Of additional interest in B is the evidence of collateral circulation, R, U, and O indicating to these investigators a significant degree of intrahepatic portal obstruction and consequent portal hypertension (From Daniel, Prichard, and Reynell J Path & Bact, vol 64, 1952)

CARDIAC FIBROSIS OF THE LIVER

As long ago as 1833, Kiernan recognized that in passive congestion due to heart disease there was a marked increase in intrahepatic connective tissue In 1886 Sabourin wrote his classic essay describing effects of chronic passive congestion on the liver and called attention to the marked capillary dilatation which was present Pick, in 1896, extended these earlier observations with his studies of the liver in pericarditis That cardiac fibrosis differed from ordinary portal cirrhosis is evidenced by the fact that Pick coined the term "pseudocirrhosis" to describe it Most of these early investigators focused their attention primarily upon parenchymal degeneration and connective tissue proliferation without paying a great amount of attention to the circulatory changes Recently, Moschcowitz has studied this particular aspect of cardiac fibrosis of the liver. He has emphasized that it is not a replacement fibrosis but is an active and proliferative process in connection with which new vascular shunts

rats and studied the circulatory pattern by means of rapid serial hepatography. Thorotrast was employed as the contrast substance. The portal pressure in these animals was increased to a degree sufficient to warrant a diagnosis of portal hypertension Hepatic angio-



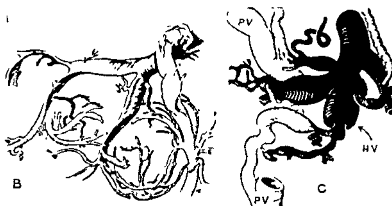


Fig 54 Reproduction of Elias, Petty, and Popper's injection studies of the cirrhotic liver In A, a photograph of an injected specimen from which the parenchyma has been digested, is shown the marked distortion of the portal and hepatic venous trees. These marked abnormalities, due to regenerating

1952)

grams obtained in these animals revealed that the intrahepatic vessels were greatly distorted Particularly were the vessels of the

In addition

al filling was

poor. ie of the dye

through the liver was not decreased, in fact it was, if anything, increased It is possible to interpret these findings as indicating that,

tumors or to an obscure form of primary endophlebitis restricted to the hepatic venous tree The disease may run a rapidly fatal course or may be slowly progressive over many years Its clinical manifestations stem from the fact that neither the portal nor the hepatic arterial blood can escape from the liver. As a result, a large collateral builds up, the manifestations of which are portal hypertension, esophagogastric varices, and hemorrhage. One of the most troublesome problems associated with this disease is the massive ascites This, of course, mirrors the experimental work which has been done on animals in which large collections of abdominal fluid can be produced at will by obstructing the inferior vena cava above the diaphragm. The massive ascites appearing in both these circumstances seems to be intimately related to abnormal intrahepatic lymph flow In addition to obstructing the hepatic veins, the thrombotic process may extend to the vena cava and obstruct this vessel near the orifices of the hepatic veins When this occurs, massive edema of the lower extremities and uremia may further complicate the picture The clinical details and pathological findings of this interesting disorganization of intrahepatic circulation have recently been ably reviewed by Caputi and Warthin

In generalized arteriosclerosis, many body systems are adversely affected Not so the liver If primary vascular disease of the hepatic vessels plays an important part in liver failure, its exact role has yet to be determined There are, of course, a number of specific afflictions of the hepatic artery or of the major hepatic vessels which, as is the case in aneurysm, may actually occur within the liver In addition, although necrotizing arteritis and periarteritis nodosa may present vascular damage in the form of infarcts within the liver, these are usually of relative unimportance as far as liver function is concerned Since such major arterial or venous diseases as occur primarily concern the function of the hepatic vessels in their extrahepatic location, their discussion will be relegated to the sections devoted to this subject

are formed within the liver. In his article on this subject, he describes four kinds of such abnormal vascular communications. those between the terminal portal venules and the central vein, those formed by new capillaries which also connect the terminal portal venules with the central veins, those between the normal portal branches and newly formed central venules, and finally those which form directly between the portal and the central veins. The apparent purpose of these shunts is to assist in the equalization of pressure between the hepatic and portal venous systems.

BILIARY CIRRHOSIS

This type of liver damage, be it either of the primary cholangiolitic type or secondary to obstruction of the common duct, has also been found to present distorted vascular relationships comparable to those seen in portal cirrhosis and cardiac fibrosis. The microscopic pathology of this disease has been ably described by MacMahon Ahrens and his associates, in reviewing 17 patients with primary biliary cirrhosis, reported that 8 developed portal hypertension. This indicates the high incidence of intrahepatic vascular abnormality which occurs in patients with biliary cirrhosis

A further comment upon abnormal hepatic circulatory dynamics in cirrhosis can be found in the recent studies of Bradley and his associates. These authors investigated hepatic blood flow by means of Bromsulphalein In the normal subject, they estimated hepatic blood flow to be 1530 ml per minute, in 39 cirrhotics this was substantially decreased, the average being 1090 ml per minute. At the same time, the hepatic arteriovenous oxygen difference increased and Bromsulphalein extraction fell. From these studies, they concluded that the blood flow through the liver decreases more than the oxidative metabolism of the residual liver cells. Thus, a relative ischemia and hypoxia of the active liver cells develops in cirrhosis.

PRIMARY VASCULAR DISEASE

[illegible]

ney, primary vascular disease may play a predominant role in malfunction Intrinsic disease of the hepatic blood vessels has, however, attracted very little attention. One of the few diseases in which one system of intrahepatic blood vessels appears to be primarily involved is the Budd-Chiari syndrome. First described by Budd in 1845 and emphasized by Chiari in 1899, this serious disruption of hepatic function occurs secondary to hepatic venous obstruction. This may be due either to occlusion of these vessels by primary or metastatic

vascular bed After the administration of one of these noxious substances, the liver becomes hugely swollen, portal pressure rises, and a large amount of blood is impounded in the splanchnic bed If a large enough dose of the drug is given, the animal dies Here again, in a somewhat different light to be sure, appears the concept that hepatic malfunction bears a definite relationship to the development and persistence of shock Over the years, the effect of a number of these related substances was intensively studied, and many theories suggested as to the mechanism by which they produced death For a longer or shorter period, one or another of these substances enjoyed a measure of popularity as the cause of shock In retrospect, it might appear obvious that both portal ligation and the administration of histamine or histamine-like substances killed by depleting the blood volume, but the idea persisted that this alone was not the answer to the perplexing physiological problem Although it could not be proved, the impression was held that in spite of the evidence to the contrary, liver failure was somehow implicated

capable of preventing death of the animal. In the study of this phenomenon, Shorr and Fine are pioneers Shorr and his associates advanced the theory that the peripheral vascular failure which is characteristic of the state of irreversibility is due to a circulatory

Fine and his associates have approached the irreversibility of shock from a somewhat different point of view They postulate that if normal oxygenation of the liver were maintained, this state could be prevented By cross transfusions from a normal animal, the circulation through the liver was kept intact These investigators then proved that in preparations such as these, the onset of irreversibility could be prevented or long delayed They concluded, as had Shorr, that the irreversibility of shock was caused by failure of normal he-

ies, Cohn and Parsons,
The former maintained

hepatic oxygenation by means of a graft interposed between the aorta and the portal vein, while the latter perfused the liver with oxygenated blood In both of these studies, the usual picture of the irreversible phase of shock could be prevented

CHAPTER 9

The Liver and Shock

IT IS difficult to determine when a relationship between the liver and death due to shock was first suspected. As long ago as 1877, Schiff, Oré, and other investigators demonstrated that if the portal vein of the dog, cat, or rabbit was suddenly ligated, the animal died within a space of minutes to an hour Many different explanations for this phenomenon were offered and widely discussed. The most generally accepted explanation was that these animals died in acute liver failure

Eck did not agree with this popular explanation and, stimulated by the reports of a physiologist from Philadelphia named Lautenbach, devised the famous fistula between the portal vein and vena cava which to this day bears his name In 1877 Eck proved beyond question that if the portal blood were diverted into the general circulation, the dog survived ligation of his portal vein quite uneventfully

With the development of the concept of shock as it is known today, greater insight was acquired as to why the dog succumbs to portal ligation in the absence of an Eck fistula. Many years later,

. . .

in shock due to depletion of the effective circulating blood volume into the splanchnic bed Literally, the dog bleeds to death into his *own portal venous system*

Another landmark in the development of the concept that some relationship exists between the liver and shock appeared in 1910 when Dale and Laidlaw investigated the depressant effects of histamine upon blood pressure Nine years later, these investigators introduced the concept of "histamine shock" Their reports started a wave of enthusiastic investigation designed to prove that autogenous vasodepressants, of which histamine was but one, were responsible under certain circumstances of severe trauma for the development of shock It was soon discovered that one of the primary sites of action of these substances was upon the intrahepatic

demonstrated the relationship of the liver to shock many years earlier

That the last word has not been written on irreversible shock is reflected in another observation originating in Fine's laboratory. Starting with the observation that many patients with overwhelming sepsis die in a state similar to irreversible hemorrhagic shock, Fine and his associates conceived the idea that a bacterial factor might well be implicated in traumatic shock. By administering aureomycin to dogs for some days prior to performing their standard type of shock-producing experiments, they report a recovery rate of 88 per cent This was in sharp contrast to the standard recovery rate of 14 per cent routinely obtained when this antibiotic was not used Currently, Fine is conducting further experiments in an attempt to find the explanation for this phenomenon In considering how far these experiments can be applied to man, it should be recalled that *the Welch bacillus is normally present in the dog's liver where it* readily proliferates if the intrahepatic oxygen tension falls below certain normal levels. This organism cannot normally be cultured from the liver of either the monkey or man In the future, it may well be proved that the feature of the irreversibility of shock is a phenomenon peculiar to the dog and related to anaerobic proliferation of noxious organisms in the liver of this animal

In 1946 Wiggers analyzed with great care the portal pressure gradients which occur in the portal system during hemorrhagic shock His experiments seem to show that during periods of hypotension, portal flow through the liver is reduced to a greater extent than might be expected from changes observed either in systemic or in portal pressure The most recent studies of this complex problem are the microscopic observations of Knisely and Seneviratne Knisely, in his studies on the frog, showed that when hemorrhage occurs the hepatic arterioles and portal venules and inlet sphincters close tightly, while the sinusoids constrict and the outlet sphincters *open Thus, the animal "gives himself a transfusion " If the hemorrhage* has not been too great, Knisely has noted that gradually a few sinusoids begin to open up and a slow trickle of blood reappears Seneviratne, employing the direct observation technique, demonstrated that a comparable phenomenon was noted in the rat's liver after hemorrhage, the sinusoids contracted and disappeared from view Seneviratne also observed the reaction of the liver to a different type of shock, namely, that produced by crushing the hind limb of an animal The initial reaction to trauma seemed to be an immediate narrowing of all the sinusoids, though the rate of blood flow continued at an unaltered pace. Slowly, however, as the shock state

By roentgenographic visualization of the liver with Thorotrast, Friedman, working in Fine's laboratory, has shown that during shock there is a severe degree of vasoconstriction of both the portal and hepatic venous beds. In Figure 56 are reproduced two of Friedman's roentgenograms illustrating this phenomenon. This investigator also observed that during shock there was increased resistance to blood flow within the liver, a rise in portal pressure, and a marked sequestration of blood in the abdominal viscera Frank, another of

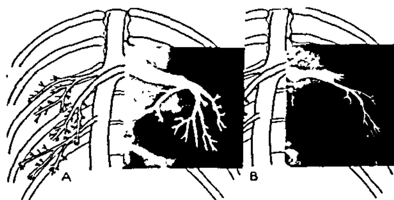


Fig 56 Friedman and Fine, in association with their extensive studies on shock, demonstrated in films such as these the marked constriction of the portal venules which accompanies this state This vasoconstriction (B) as compared with the normal liver (A) is believed by these investigators to contribute importantly to the hepatic hypoxia of shock (From Friedman et al · Ann Surg, vol 134, 1951.)

Fine's associates, then performed what may well be termed a crucial experiment In dogs with a functioning Eck fistula, he proved that the usual picture of irreversibility appeared in response to repeated bleeding despite the fact that the fistula effectively prevented the impounding of blood in the abdominal viscera Here, then, for the first time the diversity of results in the original experiments by Schiff and Eck is explained. Although dogs die when their portal veins

apparently be prevented only by maintaining hepatic oxygenation at normal levels If a degree of extrapolation be permitted, it is logical to conclude that the employment of the monkey (which does not die following ligation of its portal vein because it is equipped with its own Eck fistula) in these various experiments would have

CHAPTER 10

The Effect of Liver Disease upon Body Water

THE accumulation of excess fluid in the peritoneal cavity and in the interstitial tissue is characteristic of a variety of disorders of heart, kidney, and liver. This fluid has long been considered a transudate resulting from the passage of water, electrolyte, and protein through the capillaries of the peritoneum. Recently, however, experimental and clinical studies have indicated that at least a portion of this fluid may derive directly from the lymphatics of the liver. It represents a slightly modified extracellular fluid. The electrolyte content differs from that of serum in that sodium and chloride are somewhat higher and potassium lower. The protein content is lower and the albumin-to-globulin ratio higher. The protein content depends to some extent on the plasma level, and, as the plasma protein is depleted by successive removals of fluid containing protein, the level of protein in both plasma and ascitic fluid is reduced. Loeb, in 1922, has compared plasma to cirrhotic ascitic fluid in the same patient with respect to sodium, potassium, bicarbonate, and chloride (Table 1).

TABLE I

ELECTROLYTE CONTENT OF SERUM AND ASCITIC FLUID IN CIRRHOSIS

(From Loeb)

CASE	FLUID	CHLORIDE mEq	BICARBONATE mEq	SODIUM mEq	POTASSIUM mEq
1	Serum	100.0	27.5	124.7	4.2
	Ascitic Fluid	108.2	26.3	138.2	2.4
2	Serum	103.8	23.8	133.8	4.7
	Ascitic Fluid	109.0	23.8	126.6	2.0
3	Serum	105.6	26.4	112.2	2.7
	Ascitic Fluid	113.7	25.6	138.6	2.3

appeared, the sinusoids began to dilate and blood flow to slow down. At the time of death, the picture was one of marked dilatation and retarded blood flow. In both of these types of shock, then, the end result is the same—impaired blood flow which may be assumed to lead to deficient nutrition of the hepatic cells.

In general, then, it may be concluded that the liver indeed plays a role in shock. Although the evidence indicates that the primary factor involved is hepatocellular failure, it seems important to recognize that this is mediated through circulatory deficiencies in the organ. Any state that contributes to circulatory failure must, therefore, be regarded as exerting a deleterious effect upon hepatic function. Until proved otherwise, this state may be most logically considered due to hypoxia or even anoxia of the liver cell induced directly by circulatory failure.

pearance of ascites Some patients with seemingly minimal liver damage often present themselves with severe portal hypertension, esophagogastric varices, and massive hematemesis On the other hand, many patients with advanced liver disease are encountered in whom there is little evidence of portal hypertension, at least as judged from the fact that esophageal varices cannot be detected clinically And yet, massive ascites is often a clinical feature in these very same individuals Another indirect bit of evidence suggesting that increases in portal pressure are not in themselves responsible for ascites may be derived from patients with portal hypertension due to extrahepatic portal venous block Here ascites is rarely if ever encountered

In addition to these conflicts in the clinical course of patients with cirrhosis, there is additional evidence concerning the mechanism of ascitic fluid formation to be derived from experimental animals In the monkey, for instance, a marked elevation in portal pressure can be produced by occlusion of the portal vein It is true, of course, that

cannot be produced by portal venous [illegible]
have demonstrated that in dogs severe degrees of ascites follow partial obstruction of the vena cava just above or below its diaphragm In these preparations, there is no very great degree of portal hypertension, yet massive ascites regularly appears

Clinical and experimental examples such as these could be enumerated almost endlessly without getting very much closer to defining what role, if any, portal hypertension per se plays in the formation of ascites For the moment, it can only be said that any final conclusion on this as part of the etiology of ascites is unwarranted That the liver is primarily involved seems obvious, that the hepatic lymphatics may play an important role in the formation of ascitic fluid is a distinct, though as yet unproven, possibility

2 *Decrease in Osmotic Pressure of Blood*

Sterling in 1951 and Schoenberger in 1952 have shown that the total albumin pool as measured with tagged albumin is usually depressed in cirrhosis, though not to as marked a degree as would appear from the plasma level The very low plasma protein which results in a low osmotic pressure is due in part to dilution of blood in an expanded plasma volume, and in part to redistribution of albumin in extravascular sites It is well known that the diseased liver is unable to synthesize albumin, and plasma and albumin levels often fall as low as 2 0 to 2 5 grams per 100 ml. In such patients, Post and Patek in 1942 observed that in spite of adequate protein and

Recent experiments in which ascitic fluid has been studied with radioactive tracers have brought to light its remarkably dynamic nature. *Water of ascitic fluid enters and leaves the peritoneal cavity* at the rate of 40 to 80 per cent an hour as determined by Prentice in 1952 in his tritium studies. McKee's studies in 1952 in experimental ascites in dogs showed that albumin passed rapidly into ascitic fluid and attained an equilibrium within two days. Similar results have been obtained in man by Schoenberger *in* 1952. *With radioactively* tagged albumin, Wasserman in 1951, and Abdou in 1952, have shown in dogs and rats respectively, how rapidly albumin is equilibrated between blood and interstitial fluid. These studies support the concept that there is a continual circulation of protein from the blood stream to extracellular fluid and by way of the lymphatics back to the blood stream. In the steady state, as Mankin in 1948 showed, there is a constant colloidal and solute osmotic pressure difference between plasma and ascitic fluid which when altered is rapidly restored by transfer of water solutes or protein into or out of the cavity.

Many detailed metabolic studies have been performed to determine the cause and nature of these fluid accumulations, but even today the primary defects in ascites and edema are but poorly understood. Currently, it is the consensus that several factors rather than one are involved. Numerous studies have been made to determine the relative importance of each of these in the over-all picture. The several factors considered potentially responsible for ascites are: (1) portal hypertension, (2) decrease in the osmotic pressure of the blood; and (3) derangement of hormones which control water and electrolyte balance. These will be discussed in this order.

1 *Portal Hypertension*

Many physicians and physiologists have long held that the ascites encountered in patients with advanced cirrhosis was due to portal hypertension or, as this state was originally designated, portal congestion. There can be little doubt that this was and is an attractive concept, for it follows quite logically that as soon as hydrostatic pressure is elevated there must occur a transudation of fluid across the capillary membrane. It was, of course, upon the validity of this conjecture
ment of as[illegible]
of ascites du[illegible]
and today there is no good evidence that relief from ascites will follow the reduction of portal pressure to normal. Furthermore, in any large series of patients with cirrhosis, it is difficult to correlate the degree of hepatic damage with portal hypertension and the ap-

That the osmotic pressure of blood plays a secondary role in the etiology of ascites has been shown in numerous ways. The administration of low salt human albumin for the treatment of hypoproteinemia was first reported in 1944 by Janeway. Since then, it has been utilized by many with inconclusive results. Kunkel and his associates in 1948 stated that the replacement of albumin lost in shock or in nutritional cirrhosis is successful and may effect permanent improvement. However, when given to raise the total colloidal

TABLE 2

SERUM ALBUMIN DETERMINATION BY KJELDAHL AND IMMUNOLOGICAL METHODS IN NORMAL PATIENTS, LAENNEC'S CIRRHOSIS, AND MALNUTRITION

SUBJECT	NUMBER OF SUBJECTS	SERUM ALBUMIN KJELDAHL (K) AVERAGE IN GRAMS PERCENT	SERUM ALBUMIN IMMUNOLOGICAL (I) AVERAGE IN GRAMS PERCENT	DIFFERENCE K MINUS I AVERAGE IN GRAMS PERCENT
Normal	20	5.0	5.0	+0.05
Cirrhosis				
*Group A**	16	3.6	3.6	+0.02
Group B†	16	3.8	3.1	+0.66
Malnutrition due to malignancy, sprue, cholelithiasis, etc	12	4.3	4.2	+0.14

* Group A are cirrhotic patients who showed less than 0.3 gram per cent albumin difference between the two methods

† Group B showed more than 0.3 gram per cent albumin difference between the two methods

osmotic pressure in cases of increased portal venous pressure in cirrhosis, results have often
strong in 1948, and Post in
use Patek, and Kunkel, in
have shown that even when the plasma albumin is maintained at a normal level with large doses of human albumin, prolonged diuresis does not occur and ascitic fluid may still accumulate. On the other hand, Ralli in 1945 observed that there may be no sign of ascitic fluid accumulation in a patient whose plasma albumin is well below the normal level. These results may be due to the rapidity with which changes in water, electrolyte, and protein occur across the peritoneal membrane. As Mankin points out, when large

caloric intake, and in spite of the fact that the patient is in positive nitrogen balance, the serum albumin remains low. This suggests a definite defect in albumin synthesis in the face of normal amino acid availability for the formation of other body proteins

The plasma proteins have been studied electrophoretically by Sterling in 1949 and Franklin in 1951. These investigators found that in cirrhosis, albumin is low, gamma globulin is high, and beta globulin is also somewhat higher than normal Progressive changes toward normal in the electrophoretic pattern coincided with the clinical improvement of the patients studied. The serum albumin turnover rate and the half-life of albumin in the body have been studied in normal subjects and in patients with Laennec's cirrhosis by Sterling in 1951 and Tyor in 1952 using I^{131} tagged albumin. The serum albumin turnover rate was slower in cirrhosis than in the normal, and the cirrhotic's albumin had a longer half-life. This difference

or to cardiac failure In these, the half-life was below the normal, and the turnover rate was in the normal range It would be interesting, of course, to determine whether the albumin synthesized by cirrhotic patients is chemically different from the normal, whether a slower metabolizing component is present, or whether catabolism of albumin was delayed because of homeostatic mechanisms which tended to preserve the abnormally small amount of protein present

That albumin of cirrhotic patients may be altered is suggested by work done in our laboratory by the immunological method of Kunkel and by microkjeldahl analysis following precipitation of globulin with 23 per cent sodium sulfate by the Howe technique. Results are shown in Table 2 Three groups were studied normal subjects, cirrhotic patients, and a group of patients who were depleted of protein by malnutrition, carcinoma, or other chronic illness In about half of the group of cirrhotic patients, there was a difference of more than 0 3 gram between the albumin levels done by the two methods, and in each case where there was a difference the immunological determination was lower In the chart, the cirrhotic patients have been divided into two groups in order to show the magnitude of the difference between the two determinations There was no obvious correlation between this and the severity of the disease There appears to be a protein which is soluble in 23 per cent sodium sulfate

in cirrhosis.

That the osmotic pressure of blood plays a secondary role in the etiology of ascites has been shown in numerous ways. The administration of low salt human albumin for the treatment of hypoproteinemia was first reported in 1944 by Janeway. Since then, it has been utilized by many with inconclusive results. Kunkel and his associates in 1948 stated that the replacement of albumin lost in shock or in nutritional cirrhosis is successful and may effect permanent improvement. However, when given to raise the total colloidal

TABLE 2

SERUM ALBUMIN DETERMINATION BY KJELDAHL AND IMMUNOLOGICAL METHODS IN NORMAL PATIENTS, LAENNEC'S CIRRHOSIS, AND MALNUTRITION

SUBJECT	NUMBER OF SUBJECTS	SERUM ALBUMIN KJELDAHL (K) AVERAGE IN GRAMS PERCENT	SERUM ALBUMIN IMMUNOLOGICAL (I) AVERAGE IN GRAMS PERCENT	DIFFERENCE K MINUS I AVERAGE IN GRAMS PERCENT
Normal	20	5.0	5.0	+0.05
Cirrhosis				
Group A*	16	3.6	3.6	+0.02
Group B†	16	3.8	3.1	+0.66
Malnutrition due to malignancy, sprue cholelithiasis, etc	12	4.3	4.2	+0.14

* Group A are cirrhotic patients who showed less than 0.3 gram per cent albumin difference between the two methods

† Group B showed more than 0.3 gram per cent albumin difference between the two methods

osmotic pressure in cases of increased portal venous pressure in cirrhosis, results have often been discouraging. Thorn in 1946, Armstrong in 1948, and Post in 1951, however, report good results in its use. Patek, and Kunkel, in 1948, and Faloon, and Watson, in 1949, have shown that even when the plasma albumin is maintained at a normal level with large doses of human albumin, prolonged diuresis does not occur and ascitic fluid may still accumulate. On the other hand Ralli in 1945 observed that there may be no sign of ascitic fluid accumulation in a patient whose plasma albumin is well below the normal level. These results may be due to the rapidity with which changes in water, electrolyte, and protein occur across the peritoneal membrane. As Mankin points out, when large

amounts of albumin are given intravenously, its usefulness is evanescent and limited by the speed at which it can become re-equilibrated with the albumin in the ascitic fluid

It is apparent from all studies that a low serum albumin level is not the *only* cause of ascites and that the administration of albumin will not alone cause resorption of ascitic fluid. On the other hand, Kunkel in 1948 and Post in 1951 have noted a definite gain in appetite, strength, and feeling of well being in patients who have had large intravenous doses of albumin over the course of many weeks It is possible that this effect has to do with the state of nutrition of the patient rather than with the osmotic effect of the protein injected Patek in 1937 and 1941 first showed the improvement in

speed up the disappearance of ascites and lengthen the life of the cirrhotic patient. Control patients in her series were on a similar diet and received the liver extract intramuscularly However, this therapy has not been shown to be effective by other groups, and it is not used at the present time One would expect that a crude liver extract would contain a substance or substances which might be deficient in patients with cirrhosis of the liver, and Ralli's studies support the view that liver damage is produced or at least maintained by a deficiency of some essential factor

The role of endothelial permeability in the development of ascites

to test in vivo because of the unknown area of the peritoneal surface involved Schoenberger has utilized albumin labeled with radioactive iodine to study this possibility and to test the hypothesis that states of malnutrition are associated with increased endothelial permeability to protein which may cause ascites and edema The improvement in Ralli's patients may be on this basis

As the entire subject of ascites is reviewed in the light of serum albumin deficiency, there is evidence that low levels of this substance do play a definite role in the production of excessive amounts of intraperitoneal fluid The precise nature of the mechanism whereby these two clinical states are related has not yet been clearly defined and must for the moment remain almost as much of a riddle as does the role of elevated portal pressure

3 *Hormone Imbalance*

There is increasing evidence that the abnormal behavior of the patient with cirrhosis toward salt and water is an important factor

in the production of ascites and edema Furthermore, there is evidence that a generalized endocrine disorder is at fault Normally, the plasma levels of electrolytes and the fluid compartments are main-

the temporarily deranged physiological relationships are quickly reduced to normal

Because of the importance of the kidney in water and salt balance, it would be of vital interest to know the functional ability of the kidney in cirrhosis Reports, however, of renal function in cirrhosis are conflicting Farnsworth in 1948, Sims in 1950, and Leslie in 1951 found that in this disease glomerular filtration rate and renal plasma flow were low Leslie showed that they were low in patients who were accumulating ascites, but not in those without ascites or in *those in diuresis Jones in 1952 found a high glomerular filtration* rate at night but essentially normal renal hemodynamics in twenty-four hour measurements As reported by Farnsworth and Krakusin in 1948, Borst in 1948, and Goldman in 1951, nocturnal water and sodium diuresis in patients with cirrhosis is similar to that encountered in patients with cardiac failure and glomerulonephritis Patek in 1948, Goodyer in 1950, and Epstein in 1950 reported normal kidney function It appears, then, that defective kidney function is not the primary problem in the abnormal behavior of patients with liver disease toward sodium and water Pitts in 1950, however, has stated that small reductions in filtration rates can affect inordinately the degree of water and sodium retention Thus, with such different viewpoints and opposing observations on the role of the kidney it would appear that it cannot be entirely responsible for the accumulation of ascites

That the fluid compartments are abnormal in cirrhosis has been

is often within normal limits because of the low red cell volume When ascites and edema are present, the extracellular space is naturally greatly expanded We have studied a group of 7 patients with

using the method of Schloerb was within normal limits This observation, however, does not have much significance in view of the large range of normal values for the total body water and the difficulty of estimating the fat content of the non-aqueous portion of the body However, we did find that the ratio of extracellular fluid

(as measured by radioactive sodium dilution) to total body water

the question of the validity of the method when comparing normal and cirrhotic patients since, as we have said, sodium metabolism is altered in the disease. This small number of observations can only be considered as preliminary to the further elucidation of sodium metabolism in cirrhosis.

The hormones that have been thought to contribute to ascites formation in cirrhosis are those of the adrenal and the pituitary glands The adrenal mechanism concerns the retention of sodium by the kidney tubules and is brought about by the group of adrenal cortical hormones Normally this process is adjusted to the needs of the patient, and any excess of adrenal corticoids is disposed of by detoxification in the liver. The antidiuretic hormone of the posterior pituitary is the other endocrine involved; it is secreted when certain postulated osmoreceptors have been stimulated by a rise in total effective osmotic pressure of the blood. The hormone effects an increased water reabsorption by the kidney tubules, thereby concentrating the urine and conserving water in order to dilute the blood to a normal osmotic pressure. On the other hand, if the body is over-hydrated the antidiuretic hormone will be inhibited and a dilute urine will be excreted. Volume receptors are also postulated which will prevent a low salt diuresis if the effective blood volume is depressed These volume receptors are believed to be associated with the vascular system and to be situated in the cephalad portion of the body.

It is possible and profitable to discuss water and electrolyte balance in cirrhosis in terms of derangement of these hormones. The

stulated by Gabuzda in 1950,

1952, as the primary mecha-

That it is an adrenal steroid is

a real possibility since, as Gordon in 1952 has stated, some adrenal steroids do increase the sodium reabsorption from the kidney tubules

abnormalities occur in cirrhosis, and these have been explained on the basis that the cirrhotic liver is unable to detoxify some of the estrogens The decreased ability of the liver to detoxify a steroid "sodium-retaining factor" secreted by the adrenal is therefore probable, though such conjecture has not yet been put to the test by studies of adrenalectomized cirrhotic animals

The retention of sodium by patients with cirrhosis is a general phenomenon which Berger, in 1952, and Bongiovanni have shown includes not only an abnormally high reabsorption of sodium by the kidney tubules, and in fact often a total absence of sodium in the urine, but also a depressed sodium excretion in saliva, sweat, and intestinal secretions. This again suggests a generalized defect in metabolism Farnsworth in 1948 and 1949 found that the sodium retention in cirrhosis is greater than the retention of chloride, and that the retention of these ions is independent of the plasma concentration of sodium It has been suggested that the stimulus to retention is probably the same in both cardiac and cirrhotic patients

In the normal subject, there is a maximum output of water, sodium, potassium, and creatinine in the daytime and a minimal output at night. Sirota in 1950 has shown that this is a result of a decreased urine flow and an increased tubular reabsorption at night, but the physiological cause for this finding is not understood Goldman, Jones, and Popper, in 1952, have shown in controlled experiments that in patients with cirrhosis this daily cycle is not observed and more water and electrolytes are excreted at night than in the day The abnormality could be elicited even in patients who were in spontaneous diuresis if salt was restricted A similar aberration occurs in the ascites and edema of cardiac decompensation The phenomenon could be explained in cardiac patients on the basis of cardiorenal hemodynamics, but this explanation cannot be applied to cirrhotic patients, and it is possibly an endocrine phenomenon Rosenbaum in 1952 has shown that cortical extract administration will reverse the diurnal excretion rhythm in the normal This is further indirect evidence that increased cortical hormones are involved in the similar abnormality in cirrhotic and cardiac patients

A decreased urine output in cirrhosis was first reported by Gilbert in 1910 Adlersburg in 1943, Popper in 1952, Ralli in 1951, and Leaf in 1952 utilized various water tolerance tests to examine the physiology of diuresis in the normal and cirrhotic patients Test doses of water were ingested, and the time and the extent of the resulting diuresis measured In the normal patients diuresis occurred immediately, whereas in cirrhosis there was delayed excretion of the test dose This was well illustrated in experiments done in this clinic using the tolerance test devised by Fremont-Smith Every half hour the subjects ingested 200 ml of water and voided, the urine being collected and measured Diuresis began in the normal individual within one hour of the beginning of the test, and excretion kept up with intake, whereas a patient with cirrhosis excreted a smaller and smaller fraction of the water taken in throughout the test, and

(as measured by radioactive sodium dilution) to total body water was elevated slightly but consistently in these patients. In normal patients this ratio was 46 per cent, while in those with cirrhosis it was 54 per cent. The use of sodium to study extracellular space raises

altered in the disease This small number of observations can only be considered as preliminary to the further elucidation of sodium metabolism in cirrhosis

The hormones that have been thought to contribute to ascites formation in cirrhosis are those of the adrenal and the pituitary glands The adrenal mechanism concerns the retention of sodium by the kidney tubules and is brought about by the group of adrenal cortical hormones Normally this process is adjusted to the needs of the patient, and any excess of adrenal corticoids is disposed of by detoxification in the liver The antidiuretic hormone of the posterior pituitary is the other endocrine involved, it is secreted when certain postulated osmoreceptors have been stimulated by a rise in total effective osmotic pressure of the blood. The hormone effects an increased water reabsorption by the kidney tubules, thereby concentrating the urine and conserving water in order to dilute the blood to a normal osmotic pressure On the other hand, if the body is over-hydrated the antidiuretic hormone will be inhibited and a dilute urine will be excreted Volume receptors are also postulated which will prevent a low salt diuresis if the effective blood volume is depressed These volume receptors are believed to be associated with the vascular system and to be situated in the cephalad portion of the body

It is possible and profitable to discuss water and electrolyte balance in cirrhosis in terms of derangement of these hormones. The

stulated by Gabuzda in 1950,

1952, as the primary mecha-

That it is an adrenal steroid is a real possibility since, as Gordon in 1952 has stated, some adrenal steroids do increase the sodium reabsorption from the kidney tubules and Bongiovanni in 1951 has observed high corticoid levels in the urine of cirrhotic patients Lloyd in 1948, Bongiovanni, and Dohan in 1952 have reviewed the ample clinical evidence that endocrine abnormalities occur in cirrhosis, and these have been explained on the basis that the cirrhotic liver is unable to detoxify some of the estrogens. The decreased ability of the liver to detoxify a steroid "sodium-retaining factor" secreted by the adrenal is therefore probable, though such conjecture has not yet been put to the test by studies of adrenalectomized cirrhotic animals.

that it involves complex speculation as to the nature of the volume receptor Especially is this so when considered in light of the fact that the extracellular volume and blood volume are increased in cirrhosis and that there is no good evidence for the suggestion that peripheral effective blood volume is reduced

Eisenmenger in 1952 explains the presence of antidiuretic hormone in the relatively dilute plasma in cirrhosis by saying that in this disease the patient has become adapted to a new low plasma sodium level which is somewhat raised on the ingestion of salt and, because of the salt-retaining abnormality, there is thus a constant stimulus of the osmoreceptors for antidiuretic hormone production This eliminates the necessity of postulating volume receptors The consensus at the present time, as voiced in this laboratory as well as by Gordon in 1951 and Ralli in 1951, is that the sodium-retaining effect stimulates the excessive secretion of the antidiuretic hormone This gives rationale to the current and most effective symptomatic treatment for the disease, namely, restriction of sodium This regi-

THERAPEUTIC APPLICATIONS

Eisenmenger in 1949, Chalmers in 1949, Kark in 1951, Ricketts in 1951, Lowe in 1951, and Tarail in 1951 have utilized a high protein, high caloric, low sodium diet in the management of cirrhotic patients with encouraging results Layne in 1947 has used a high fluid, low salt regimen When salt is restricted, ascitic fluid accumulates more slowly or not at all For each patient, there appears to be a salt intake level which can be tolerated without accumulation of fluid As the patient improves clinically, he can tolerate increasing amounts of salt Eisenmenger in 1950 describes the recompensation of patients who have been placed on a low salt diet The first indication of improvement is a rise in serum sodium and an increased sodium excretion This occurs long before a decrease in ascitic fluid formation appears and associated fluid balance changes become obvious It is probable that the sodium retaining hormone has been reduced possibly by an improved liver mechanism for destroying the excess hormone

Other types of therapy have been attempted in this disease Portis has recently reviewed these Havens in 1950 and Hilton in 1952 have used murcurial diuretics to stimulate the discharge of ascitic fluid accumulation, but unless ammonium chloride is given with the diuretic the diuresis is minimal Cation exchange resins have been proved to have value in treatment of cirrhotic patients by

half an hour after the end of the drinking period he had excreted only 259 ml of the 1200 ml ingested

Vernay reported in 1948 that vasopressin, the antidiuretic hormone of the posterior pituitary, is secreted under the stimulus of an increased total effective solute concentration of the plasma. The organs stimulated were named "osmoreceptors," and Vernay gave evidence that they are situated in the vascular bed of the internal carotid arteries A low plasma sodium is typical of cirrhotic patients and especially those who are decompensated Amatuzio in 1952 has shown that several other plasma constituents such as potassium, calcium, and phosphate, as well as protein, are also low. In fact, the blood appears to be generally diluted However, Dochios in 1951, Ralli in 1951, Hall in 1949, Sims in 1950, Drill in 1948, and Robinson in 1950 measured blood and urinary antidiuretic hormones during the course of water tolerance tests of the kind described above and showed that in spite of the low plasma sodium level and the test load of water, this hormone could still be identified in the urine of patients with cirrhosis as well as in the urine of patients with edema from other conditions On the other hand, this hormone was absent in the normal overhydrated subject White in 1951 and Nelson in 1952 have shown that the sensitivity of osmoreceptors to changes in solute concentration was not increased in cirrhotic patients and that their ability to destroy vasopressin was normal. These investigators therefore concluded that the hormone was produced in increased amounts. Typical signs of decompensating liver disease including hyponatremia and edema resulted when Lyons and Lloyd in 1951 injected daily doses of vasopressin into cirrhotic patients No such effect, however, was noticed in the normal This was taken as additional evidence that some of the symptoms in cirrhosis can be explained on the basis of an increased antidiuretic hormone secretion

The abnormal output of antidiuretic substances in the presence of a low plasma sodium is not confined to cirrhosis but is noted in several other conditions Leaf in 1952 has observed it in (1) Addison's disease, (2) patients with congestive heart disease, (3) dogs depleted of extracellular fluid electrolyte by peritoneal dialysis, and (4) dogs given small amounts of vasopressin He suggests that two receptor mechanisms are involved: one is sensitive to total effective solute concentration and stimulates osmoreceptors to secrete the antidiuretic hormone when solute concentration is high; the other is sensitive to volume changes in a crucial portion of the extracellular fluid Lewis in 1950 and Strauss in 1952 suggest that the latter receptor is probably intravascular and has priority over the osmoreceptor mechanism so that in spite of a dilute plasma, diuresis does not occur. This seems like a clever explanation for the facts except

latter hormone will be excreted under the stimulus of excessive sodium retention, and water will be retained These are only a few of the hormones which are known to take part There may be others

Although recent studies have uncovered many new facts in this field, the importance of the various factors in liver disease is not yet known, and very little has been accomplished as yet along the lines of using this new information for effecting anything but palliation in the treatment and management of chronic liver disease Relief of bleeding esophageal varices has been accomplished by portacaval shunts, but no surgical procedure is known for the prevention of ascites Many investigators have found that a high calorie, high protein, high vitamin regimen seems to benefit these patients. Perhaps the most important single element in their treatment is the restriction of salt intake The impression has been gained by some investigators that if the patient is able to tolerate a low salt regimen and still keep to a nutritive diet, the disease process is actually delayed This may be merely due to the retardation of fluid accumulation and the prolongation of time before wasteful paracenteses become necessary

Irwin in 1949, Hay in 1950, Rosenak in 1952, and Best in 1952, but Gabuzda in 1952 has shown that they were often not tolerated and could lead to low salt syndrome, acidosis, nausea, and vomiting There is no indication that mercurials or resins do anything to improve the liver function or the clinical course of the patient In fact, they may do harm by dangerously depleting the tissue of salts.

Recently, Habif, Randall and Soroff have reported a series of 15 patients with cirrhosis and ascites who were also candidates for portal decompresion As a result of their carefully documented studies, they concluded that the most important single defect is sodium retention In 10 of these patients, ascitic fluid control was achieved through restricted sodium intake; in 5 ion exchange resins

to be prevented Resins, although not without danger, can, these investigators believe, contribute materially to the rapidity with which ascites may be brought under control in those patients urgently requiring a portacaval shunt

It is apparent that the liver functions indirectly in the control of body water in several different ways. A study of the patient with a diseased liver shows that the liver is involved in the maintenance of vascular pressure relationships, protein synthesis, and endocrine balance—all of which affect the control of water and salt in the body. The intrahepatic vascular system must be normal to handle the large volume of blood which constantly flows through it When scarring of liver parenchyma occurs, liver vessels and lymphatics may be occluded and a high portal pressure may result Then ascites will occur, and although portal hypertension is known not to be the most important factor in ascites, it undoubtedly contributes to it The most important blood protein from the osmotic point of view is plasma albumin which is believed to be manufactured solely by the liver. Here again a deficient, and possibly defective, albumin synthesis by the liver is not alone responsible for the large accumulations of ascites and edema fluid in liver disease However, the decrease of effective osmotic pressure as a result of the low plasma albumin level must play a role in accelerating the accumulation of fluid in extravascular areas. The mechanisms in the liver which detoxify hormones form an integral part of the delicate balance of salt and water which normally exists in the body. A defective liver may be unable to destroy the adrenal cortical hormones which effect the retention of sodium The increased sodium retention which results from the excess of this hormone will cause an imbalance of another hormone, namely, the antidiuretic hormone of the posterior pituitary This

been shown upon innumerable occasions to inhibit hepatic repair (Vars and Gurd, Gurd, Ravdin and Gars)

That hepatic regeneration bears a definite relationship to certain *endocrine functions* has been demonstrated by numerous investigators (Berman, Sylvester, Hay and Selye, Rapport, Canzanelli and [illegible] of hypophysectomy is direct or mediated through the adrenal In adrenalectomized rats, for instance, the ability of the liver to regenerate can be restored by adrenal cortical extract or desoxycorticosterone If desoxycorticosterone is administered to normal rats, ex-

of the hepatic duct, the liver remaining after partial hepatectomy regenerates but little if at all It is not known whether this reduction in regenerative capacity is a manifestation of parenchymatous damage or secondary to the reduction in hepatic blood supply which occurs in cirrhosis

Hepatic regeneration has been studied extensively under conditions of *altered blood supply* The most dramatic of these concerns diversion of the portal blood away from the liver (Milne in 1909 Mann and Magath in 1922, Mann, Fishback, Gay and Green in 1931, Stephanson in 1932, Grindlay and Bollman in 1952, Child, Barr, Holswade and Harrison in 1953), either by partially constricting or ligating branches of the portal vein or by creation of an Eck fistula Under these circumstances, the normal liver becomes atrophic, and if the experiments are performed in young animals, the liver fails to grow to normal size In animals with an Eck fistula, the liver tissue remaining after partial hepatectomy fails completely to restore itself as it does in normal animals The reason for this apparent dependence of hepatic growth and regeneration upon an intact portal circulation has been the subject of extensive discussion and experimentation The adverse effects of diversion of portal blood away from the liver have been related by some to an as yet unidentified factor in portal blood and by others to reduction in total hepatic blood flow

A number of attempts have been made to demonstrate a relationship between *blood flow* and hepatic regeneration Higgins, Mann and Priestley in 1932 combined partial hepatectomy in fowl with ligation of the postcaval vein Fowl were chosen because there

CHAPTER 11

Hepatic Regeneration

AS RECENTLY as 1898, Aschoff expressed the belief that all or-

indeed able to restore itself to normal by a biological process which could only be interpreted as regeneration. The evidence of this was derived not only from the study of diseased human livers, but also from various experiments performed upon numerous species of animals For instance, Ponfick and von Meister in 1894 were among the first to resect large portions of the liver in dogs and to demonstrate that regeneration took place from the hepatic remnants. These investigators pointed out that the hepatic lobes which were permitted to remain increased several fold in size. In addition to establishing the capacity of the liver to regenerate, they also demonstrated that this capacity was of considerable proportion. In 1929 Fishback carried experiments of this type from the qualitative to the quantitative and showed that even after repeated resections of hepatic tissue in dogs, the liver was able within a matter of weeks to restore itself to its original weight

FACTORS AFFECTING REGENERATION

Once the ability of the liver to restore itself was recognized, numerous experimental efforts were made to modify the regenerative process The effects of diet, endocrine deficiencies, biliary obstruction, cirrhosis, and alteration in hepatic blood supply have all been

to regeneration and that animals fed high fat diets were capable of restoring their livers to normal provided adequate protein and lipotropic factors were added to the diet Davis and Whipple also demonstrated that proteins, while supporting regeneration, were not as effective as carbohydrates. On the other hand, protein depletion has

in 1945, Benz, [illegible] the left lobe [illegible] period of life, [illegible] the right lobe. At birth the ductus venosus closes, routing the major portion of the afferent hepatic venous blood through the right lobe The left lobe decreases in relative size as the right lobe enlarges In humans, atrophy of the left lobe of the liver has been reported several times Perhaps the largest series is that of Benz, Baggenstoss and Wollaeger, who described 32 cases in 60 per cent of which they found anatomical evidence of compromise of the left main branch of the portal vein It would appear, therefore, that the liver in humans, as in other species, is dependent upon an intact venous supply

Because the question of which was the most important factor in hepatic regeneration—portal blood flow or simply venous blood flow—did not appear to have been answered conclusively, a series of experiments designed to throw more light upon this perplexing problem have recently been performed in the surgical laboratories of The New York Hospital There it was postulated that if all portal blood could be excluded from the liver and at the same time a copious flow of systemic venous blood maintained, some more definite conclusions might be reached This was accomplished by an animal preparation in which the portal and caval blood flows were transposed In a series of dogs, the caudal end of the portal vein was sutured to the cephalic end of the abdominal vena cava, and the cephalic end of the portal vein similarly sutured to the proximal end of the divided vena cava (Fig 57) In such a preparation, all the portal blood is diverted away from the liver, while all of the systemic venous blood from the hind part of the animal passes through the liver After the animals had recovered from this operation, a 70 per cent hepatectomy was performed, and the course of the hepatic remnants followed closely As nearly as could be determined, the lobes remaining after hepatectomy regained 20 to 80 per cent of the weight of the resected liver The average was 50 per cent with a standard deviation of 21 The complete details of these experiments are recorded in Appendix 6

The degree of hepatic regeneration (50 per cent) observed in these animals in which the portal and caval circulations had been transposed is considered significant Particularly is this true since normal dogs regenerate their livers completely after partial hepatectomy, whereas dogs with an Eck fistula are completely incapable of hepatic

exists in these birds a natural anastomosis between the postcaval and hepatic portal venous systems via the inferior mesenteric vein. Ligation of the postcaval vein in effect produced a reverse Eck fistula There then followed greater hepatic regeneration than was anticipated This was interpreted as due to an excessive volume of venous blood coursing through the liver Grindlay and Bollman in 1952 did not confirm this observation in dogs where, in the presence of a reverse Eck fistula, hepatic regeneration after partial hepatectomy was no greater than normal. In spite of this, Mann, Bollman and Grindlay have long supported the hypothesis that liver regeneration is dependent upon an abundant supply of venous blood although this need not necessarily be portal.

In 1940 Mann, attempting to relate hepatic regeneration to the presence or absence of portal blood, performed partial hepatectomy in dogs with side-to-side portacaval shunts He found that when the shunts were patent, liver regeneration was decreased as compared with normal dogs but greater than in dogs with Eck fistulas. He drew [illegible] factor in it was responsible for the regeneration seen. In the normal dog, partial hepatectomy diverts the entire portal flow into a reduced hepatic ca[illegible] regeneratio[illegible] enlarge. A side to side portacaval shunt provides an outlet for the relative excess of portal blood created by partial hepatectomy. It has been reasoned that since portal pressure does not rise as high, less regeneration occurs

Grindlay and Bollman (1952) reported that constriction of the thoracic inferior vena cava promoted liver regeneration after partial hepatectomy in dogs with classic Eck fistulas. Restriction of blood flow in the inferior vena cava below the liver also stimulated regeneration in these dogs Compression of the portal vein impaired liver regeneration after partial hepatectomy, but when this was released or combined with caval constriction above or below the liver, additional regeneration occurred It is easy to visualize how partial caval obstruction above the diaphragm might produce increased hepatic venous filling and so account for the regeneration found. Why this should occur with caval constriction below the diaphragm is less [illegible]

Certain observations made during the prenatal development of sheep and humans are pertinent (Barclay, Franklin and Prichard

likelihood of the existence of a portal factor, specific for 100 per cent regeneration, has diminished in the light of the information obtained from these experiments, it has not been excluded. Obviously, a greater number of experiments such as these must be performed under carefully controlled conditions before any decisive conclusions can be reached.

While both nutritional and endocrine deficiencies as well as intrinsic disease inhibit liver regeneration, it appears that the state of the hepatic circulation exerts a dominant influence. There is, at present, very little information regarding the role of the hepatic artery, attention in the past having been focused upon the portal system. Since, in terms of total blood flow, the portal vein supplies upwards of 70 per cent of hepatic blood, it may be that the venous component is more important than the arterial in this phase of liver physiology. The fact that liver atrophies and fails to grow or regenerate in the absence of venous blood lends support to this belief. Yet the assumption that portal blood itself is required is unwarranted for, as has been demonstrated in the dogs with portacaval transposition, systemic venous blood can support liver regeneration. It follows, then, that it is a requirement by the liver for a minimal quantity of venous blood that must be fulfilled. This the portal vein supplies in health. It may or may not in disease. It is therefore intriguing to speculate upon the possibility that the primary effect of certain pathological processes upon the hepatic vasculature may in large part be responsible for secondary changes in hepatic structure and function as reflected in atrophy, failure of regeneration, or hepatic insufficiency. The vascular changes resulting from nutritional and endocrine deficits are not obvious, but that these do occur following biliary obstruction and in cirrhosis has been demonstrated many times.

THE NATURE OF REGENERATION

Certain basic questions pertaining to liver regeneration have been deliberately avoided up to this point. These concern why liver regenerates in the first place, what the stimuli are, why it stops when it does, and whether regeneration is a precursor of carcinoma. The

a 70 per cent hepatectomy. The marked regeneration of the 30 per cent remnants can readily be discerned by comparing C and E.

1. Degree of hepatic regeneration obtained following 70 *per cent hepatectomy* in dogs with normal and transposed portacaval circulations. For these comparisons dogs of nearly equal weight were selected. In 1 is shown the hepatic remnant left after 70 per cent hepatectomy, in 2 the amount of regeneration after six weeks in a dog with transposed portacaval circulations, and in 3 the degree of regeneration appearing after a similar length of time in an animal with normal portal circulation (see text).

B C IVC PV A D E



similar portal venograms obtained one week, four weeks, and six weeks after

CHAPTER 12

The Extrahepatic Splanchnic Circulation

EACH minute a volume of blood approximately equal to one quarter of the cardiac output passes through the liver. The source of this large amount of blood is unequally divided between the portal vein and the hepatic artery, the portal blood finds origin in the splanchnic venous bed and is delivered to the liver under low pressure, while that from the hepatic artery reaches the liver directly from the aorta and arrives under high pressure. The relative proportions of venous and arterial blood reaching the liver were thought at one time to be fixed in amounts, but recently evidence has accumulated indicating that this ratio varies in response to both hormonal and nervous controls. Thus the liver, bathed internally in a large volume of blood of varying composition, carries on its many functions all of which are essential to normal bodily economy. In order to discharge effectively its destiny and to deal successfully with two quite different sources of blood entering it under widely divergent pressures, the liver has developed the highly specialized internal vascular arrangement outlined in the previous chapters. It is the purpose of these sections to consider the anatomy and some of the physiological features of the three blood systems comprising the inflow and outflow pathways of the liver.

GROSS ANATOMY

The Portal Venous System

The portal venous system, unique in that it is bounded by two capillary beds, consists primarily of the portal, superior mesenteric, and splenic veins. These major channels, although remarkably constant in their general anatomical relationships with neighboring structures, vary somewhat in size and length. At relatively inconstant locations they receive the cystic, coronary, inferior mesenteric, and pancreatic veins. Anomalies of the major constituents of this system, though they occur, are rare and have been discussed in a previous chapter. Because of the recently renewed interest in portal decompression in the treatment of portal hypertension, several extensive

earliest writers viewed the processes of liver regeneration as compensatory hyperplasia and hypertrophy in response to functional demand. Yet all animals are endowed with more liver tissue than they actually need. This is at least implied in the somewhat teleological statement that the liver has great functional reserve. It is possible that what really is meant is that the liver possesses great reserve because of its regenerative capacity. Mann disputes the theory of functional demand because of the complexity of the liver and its multiplicity of functions. He believes that the stimulus to liver regeneration is blood flowing through the intrahepatic vascular bed under increased pressure, regeneration occurring passively as the hepatic vascular bed enlarges.

Factors similar to these must also be concerned in the transposition from hyperplasia to neoplasia, but at present their precise roles are obscure. The frequent coincident occurrence of cirrhosis, in which regeneration is such a prominent feature, and hepatoma both in humans and in laboratory animals points towards a relationship between these two pathological states, but beyond this little can be said. Unfortunately, in the present state of our knowledge and understanding, the questions raised must remain largely unanswered.

CHAPTER 12

The Extrahepatic Splanchnic Circulation

EACH minute a volume of blood approximately equal to one quarter of the cardiac output passes through the liver The source of this large amount of blood is unequally divided between the portal vein and the hepatic artery, the portal blood finds origin in the splanchnic venous bed and is delivered to the liver under low pressure, while that from the hepatic artery reaches the liver directly from the aorta and arrives under high pressure The relative proportions of venous and arterial blood reaching the liver were thought at one time to be fixed in amounts, but recently evidence has accumulated indicating that this ratio varies in response to both hormonal and nervous controls Thus the liver, bathed internally in a large volume of blood of varying composition, carries on its many functions all of which are essential to normal bodily economy In order to discharge effectively its destiny and to deal successfully with two quite different sources of blood entering it under widely divergent pressures, the liver has developed the highly specialized internal vascular arrangement outlined in the previous chapters It is the purpose of these sections to consider the anatomy and some of the physiological features of the three blood systems comprising the inflow and outflow pathways of the liver

GROSS ANATOMY

The Portal Venous System

The portal venous system, unique in that it is bounded by two capillary beds, consists primarily of the portal, superior mesenteric, and splenic veins These major channels, although remarkably constant in their general anatomical relationships with neighboring structures, vary somewhat in size and length At relatively inconstant locations they receive the cystic, coronary, inferior mesenteric, and pancreatic veins Anomalies of the major constituents of this system, though they occur, are rare and have been discussed in a previous chapter Because of the recently renewed interest in portal decompression in the treatment of portal hypertension, several extensive

anatomical investigations of the portal venous system have been reported within the past few years. These have served not only to confirm many of the studies of older anatomists, but also to establish certain new and hitherto unappreciated anatomical facts Rousselot was perhaps the first to call attention to numerous of the deviations in standard descriptions of the portal venous system as portrayed by older anatomists Figure 58 illustrates diagrammatically the concepts of several leading anatomists—Hanrahan, Spaltcholz, Gray,

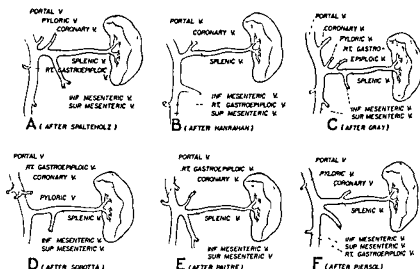


Fig. 58 In these diagrams are reproduced the concepts of the relationships of the portal, coronary, splenic, inferior and superior mesenteric as portrayed by a number of early anatomists

Paitre, Sobotta, and Pierso! It is obvious that numerous differences *in opinion appear as to the entrance into the portal circuit of the* coronary, the pyloric, and the inferior mesenteric veins The explanation for these differences can probably be found in the fact that most anatomists have based their conclusions upon one or

unfixed specimens studied were removed at routine postmortem examinations, 21 were adults and 4 were stillborn infants Gilfillan found that in his 61 dissections the portal vein was formed with

ly to the porta hepatis Here it divides to form the right and left hepatic veins, the gross anatomy of which has been discussed in an earlier section The smaller tributaries of the portal vein itself consisted primarily of the coronary, the pyloric, the cystic, and irregular pancreaticoduodenal branches Among these, the coronary system of veins is of greatest clinical interest, for it is this system that is directly related to the development of esophagogastric varices In 68 per cent of the 61 dissections, the coronary or left gastric vein entered the portal vein In the remainder it entered the splenic, either near or at its junction with the portal vein

The surgical significance of these vessels is greatest in operations in which a portacaval anastomosis is contemplated In freeing the portal vein within the hepatoduodenal ligament, great care must be exercised during dissection lest one of these small veins be torn off from the portal Not only is the hemorrhage brisk following such a disaster, but the transfixion ligature which must be used to control bleeding inevitably either compromises the size of the vein or lies directly in the suture line of the proposed portacaval anastomosis

The *splenic vein*, deriving its blood from the spleen, the stomach, the pancreas, and, in irregular instances, from the left colon and rectum, joins the superior mesenteric to form the portal Near the head of the pancreas the splenic vein may be well buried in pancreatic tissue, but for the most part it is clearly visible along the cephalic border of the pancreas All along its course it receives many small branches directly from the pancreas These short branches may be torn during either pancreatectomy or mobilization of the splenic vein preparatory to the performance of a splenorenal shunt In the latter circumstance, ligation and division of these small vessels may so seriously compromise the diameter of the splenic vein that it becomes well nigh useless for the purpose of constructing an adequate shunt Under such circumstances Rousselot has urged that an autogenous vein graft (a suitable segment of the patient's superficial femoral vein) be inserted between a useful stump of the splenic vein and the side of the renal vein

The *superior mesenteric vein*, collecting blood from the small intestine, the colon, and the head of the pancreas, is characteristically short, in fact it may consist of no more than the junction of several large mesenteric veins

The *inferior mesenteric vein*, collecting blood from the lower small intestine, the descending colon, and the sigmoid colon, irregularly enters either the splenic, the superior mesenteric, or the junction of the splenic and superior mesenteric veins Gilfillan found that this vessel entered the splenic (the position most generally shown in textbooks of anatomy) in only a little over 50 per cent,

in 43 per cent this large vein entered either the superior mesenteric or the portal vein Gilfillan's final conclusion on the variations in the morphology of the portal vein and its tributaries with the average length of each segment is reproduced in Figure 59.

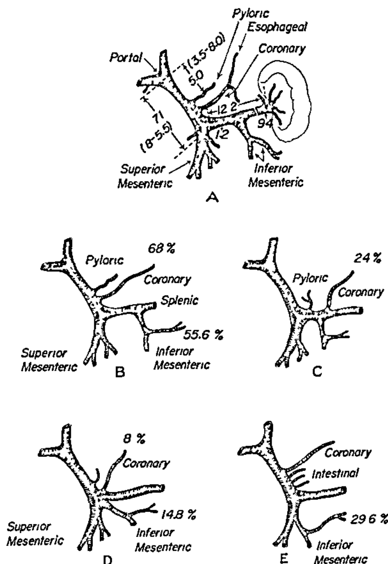


Fig 59 In these diagrams are portrayed the statistical analyses of the portal, coronary, pyloric, splenic, and inferior and superior mesenteric veins as evolved by Gilfillan (From Gilfillan. Surgery, vol 61, 1949.)

In 1951 Purcell and his associates dissected 100 fresh autopsy specimens and found that the average anatomical length of the portal vein was 7 34 cm, while the average surgical length was 4 02 cm The greatest surgical length was 7 cm, while the shortest was 2 cm The average diameter of the portal vein was 1 09 cm In studying the number of tributaries received by the portal vein, these surgical anatomists found that in only 14 per cent of their dissections was it completely free of entering venous channels In all others the cystic, coronary, or pyloric vein entered the major portal vessel In studying the splenic vein, they found even greater variations in length and size The average length was 10 54 cm, while the average diameter at the distal end was less than 0 5 cm In 44 per cent of these autopsies, the splenic vein received the inferior mesenteric vessel The average length of the superior mesenteric vein was 3 39 cm, the longest 15 cm and the shortest 1 cm The inferior mesenteric veins which did not enter the splenic either emptied into the superior mesenteric vein or entered the junction of the splenic and superior mesenteric vessels Because of its potential importance in fashioning a splenorenal shunt, these authors also studied the length and size of the superior mesenteric vein This they found to average 8 31 cm The average diameter was 0 92 cm

In 1950 Douglass, Baggenstoss, and Hollinshead, working at the Mayo Clinic, also studied the normal anatomy of the portal system of veins Dissatisfaction with standard texts and atlases of anatomy led them to an analysis of 92 necropsy specimens for the purpose of determining the percentage incidence of major variations in the portal vein and its afferent vessels They noted that the splenic vein was formed by the convergence of a number of short splenic trunks In 7 of their specimens, they found an excessively long splenic trunk which was of sufficient diameter to have served admirably in fashioning a splenorenal shunt The opinion of these investigators upon the further disposition of the splenic vein differed somewhat from that of Purcell They believed that the splenic vein was frequently so completely encased in pancreas that its mobilization for purposes of a shunt would have been well nigh impossible These men found the average postmortem diameter of the splenic vein to be 0 45 cm, a size hardly large enough to encourage enthusiastic fashioning of a splenorenal shunt The inferior mesenteric vein was variable in its termination, it entered either the superior mesenteric the splenic or at the point of junction of these two vessels The portal vein was found to receive the splenic and superior mesenteric as generally described The only variation from standard representations consisted in the fact that its length was 6 4 cm, somewhat shorter than usually described The coronary generally terminated at the junc-

tion of the superior mesenteric and splenic veins, though in 24.4 per cent of the dissections it entered the portal, while in 16 7 per cent it entered the splenic. Douglass, Baggenstoss and Hollinshead's concept of the portal system of veins is reproduced in Figure 60

In general, then, the normal anatomy of the portal splenic and superior mesenteric veins is remarkably constant and anomalies are rare It is obvious from the many measurements which have been

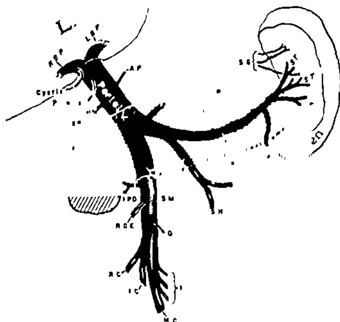


Fig 60 Detailed anatomy of the portal venous system (From Douglass, Baggenstoss, and Hollinshead Proc Staff Meet, Mayo Clinic, vol 25, 1950)

taken that normally these vessels are not of any very great diameter. Were portal decompression necessary in a normal individual, the question might readily be asked whether these vessels might not be too small to yield venovenous shunts large enough to carry important amounts of blood Furthermore, it might be postulated that shunts of such small caliber would close promptly Fortunately, portal hypertension of sufficiently long standing to produce varices and hemorrhage is associated with an appreciable enlargement in the diameters of both the portal and splenic veins In patients with cirrhosis, portal veins have been encountered with diameters of 2 cm So common is this finding that it provides considerable assurance that an adequate shunt of large caliber can be fashioned for purposes of portal decompression If the portal vein can be relied upon to

enlarge in cirrhosis, the splenic vein cannot. Although occasionally the vessel may reach a diameter of 2 cm., it more frequently is less than 1 cm. It is this lack of reliability in the size of the splenic vein which has persuaded many surgeons to abandon direct splenorenal

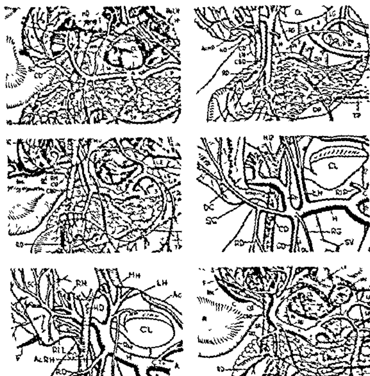


Fig. 61. Michels has made many important contributions to knowledge of the gross anatomy of the hepatic artery. In the above diagrams are represented random samples of this anatomist's dissections.

anastomoses in favor of the portacaval variety. The size, of course, of the splenorenal shunt can be increased if a vein graft is employed.

The Hepatic Artery

As emphasized in the section on embryology and anomalies, the hepatic artery presents a much greater degree of variation than is encountered in the portal venous system. The most authoritative article on this subject is that of Michels, and the salient features of his many dissections are outlined in Figure 61. Recently Johnston and Anson performed detailed dissections of the hepatoduodenal ligament. Although these authors directed their attention primarily

tion of the superior mesenteric and splenic veins, though in 24 4 per cent of the dissections it entered the portal, while in 16 7 per cent it entered the splenic. Douglass, Baggenstoss and Hollinshead's concept of the portal system of veins is reproduced in Figure 60.

In general, then, the normal anatomy of the portal splenic and superior mesenteric veins is remarkably constant and anomalies are rare It is obvious from the many measurements which have been

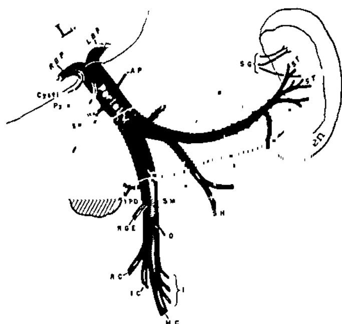


Fig 60 Detailed anatomy of the portal venous system (From Douglass, Baggenstoss, and Hollinshead Proc Staff Meet, Mayo Clinic, vol. 25, 1950)

taken that normally these vessels are not of any very great diameter. Were portal decompression necessary in a normal individual, the

pertension of sufficiently long standing to produce varices and hemorrhage is associated with an appreciable enlargement in the diameters of both the portal and splenic veins. In patients with cirrhosis, portal veins have been encountered with diameters of 2 cm. So common is this finding that it provides considerable assurance that an adequate shunt of large caliber can be fashioned for purposes of portal decompression If the portal vein can be relied upon to

enlarge in cirrhosis, the splenic vein cannot. Although occasionally the vessel may reach a diameter of 2 cm., it more frequently is less than 1 cm. It is this lack of reliability in the size of the splenic vein which has persuaded many surgeons to abandon direct splenorenal

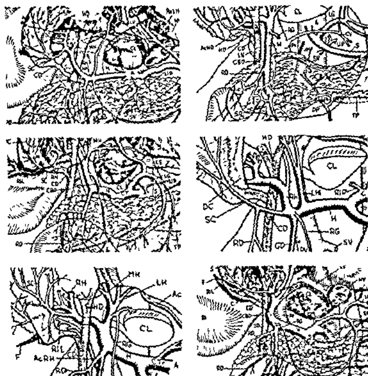


Fig. 61. Michels has made many important contributions to knowledge of the gross anatomy of the hepatic artery. In the above diagrams are represented random samples of this anatomist's dissections.

anastomoses in favor of the portacaval variety. The size, of course, of the splenorenal shunt can be increased if a vein graft is employed.

The Hepatic Artery

As emphasized in the section on embryology and anomalies, the hepatic artery presents a much greater degree of variation than is encountered in the portal venous system. The most authoritative article on this subject is that of Michels, and the salient features of his many dissections are outlined in Figure 61. Recently Johnston and Anson performed detailed dissections of the hepatoduodenal ligament. Although these authors directed their attention primarily

toward the extrahepatic bile ducts, their concomitant observations upon the hepatic artery and portal vein are invaluable to surgeons called upon to work in this area. So excellent are their illustrations that they are reproduced in Figure 62.

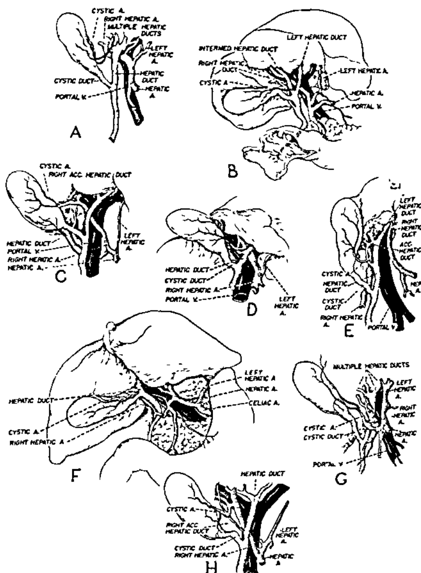


Fig 62. In this extensive series of diagrams are reproduced diagrammatically the results of Johnston and Anson's extensive studies upon the variations from the normal of the extrahepatic segments of the hepatic artery. (From Johnston and Anson Surg, Gynec. & Obst, vol. 94, 1952.)

The Hepatic Veins

In their extrahepatic positions, the hepatic veins are so short that any detailed anatomical description of them is quite unnecessary Suffice it to state that these vessels have been approached surgically on such rare occasions that not one reference to their anatomical relationships can be found save those occurring in standard text books of anatomy Furthermore, it seems unlikely that these vessels will ever become important surgically

MICROSCOPIC ANATOMY

The Portal Venous System

The veins of the portal system are relatively thin-walled compared with those of the systemic venous circuits and generally do not contain valves. These anatomical characteristics undoubtedly stem from the fact that they are rarely called upon to withstand a very great degree of pressure The walls of the portal vein, and to a lesser extent those of the superior mesenteric and splenic veins, do, however, contain well developed elastic and muscular coats In the portal vein of man can be found a definite elastica interna with fibers running both in a circular and in a longitudinal direction Collagen also is present though its amount varies from region to region in the splanchnic bed As soon, however, as the portal vein enters the liver, it quickly loses its muscular, collagen, and elastic tissue coats As it is followed to its smaller and smaller radicles, the point is reached where, at a caliber of a millimeter or so, all evidence of muscular coats disappears Its final branches, the walls of the sinusoids, are but one cell thick The gastric veins have a thick inner layer of circular muscle fibers intimately intertwined with longitudinal elastic tissue fibers and a wide outer layer of collagen and circular elastic fibers The splenic vein, on the other hand, is possessed of an extensive circular muscular coat but only a few longitudinal fibers The hepatic veins have been extensively studied in both man and lower animals because of the apparent role this vascular circuit plays in regulating hepatic blood flow In man, these vessels are believed to be relatively devoid of smooth muscle until the larger constituents are reached Near the vena cava large muscle bundles can be easily identified In the dog these are, of course, particularly well developed

Brendle has summarized the microscopic anatomy of the portal venous system as follows Working from the peripheral splanchnic capillary bed toward the liver there are progressively fewer circular muscle fibers and a relatively greater number of longitudinal fibers Throughout most of the extent of the portal vessels, the elastic fibers are arranged longitudinally In the portal vein itself, however, there is a well developed circular elastic coat Brendle's concept concurs

toward the extrahepatic bile ducts, their concomitant observations upon the hepatic artery and portal vein are invaluable to surgeons called upon to work in this area So excellent are their illustrations that they are reproduced in Figure 62

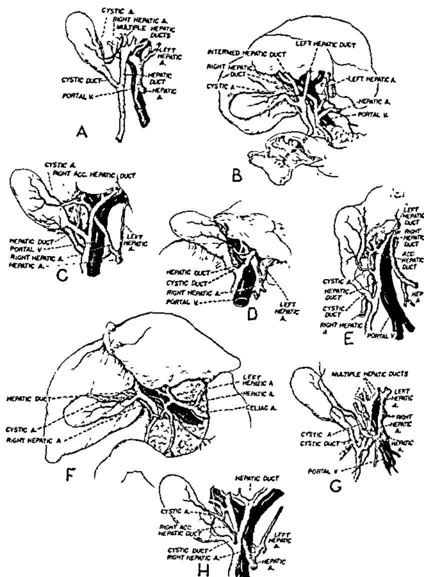


Fig. 62. In this extensive series of diagrams are reproduced diagrammatically the results of Johnston and Anson's extensive studies upon the variations from the normal of the extrahepatic segments of the hepatic artery (From Johnston and Anson Surg, Gynec. & Obst., vol 94, 1952)

upon to shunt blood directly into the portal venous bed at such times as it is not needed for enteric absorption and transport Spanner studied these mechanisms extensively and concluded that in man the shunt lies in the villus itself As the hepatic arteriole reaches the tip *of the villus, it breaks up into two branches, one supplying the* capillary bed and the other emptying directly into a portal venule During alternate periods (fasting and absorbing), blood circulates

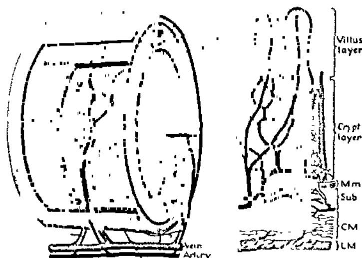


Fig 63 Circulatory arrangements in the small intestine Although the hepatic capillary bed has been the object of many investigations, this other portal capillary bed has been relatively unstudied in so far as its relationship to portal hemodynamics are concerned Of particular interest is the fact that under certain circumstances of stress, huge amounts of blood can be shunted past the capillary bed of the intestinal tract and delivered directly to the liver (From Maximow and Bloom Textbook of Histology)

either through the capillary bed of the villus or is dumped directly into the portal venous system In the cat and dog, however, Spanner believes a different mechanism is present In these animals, there are *arteriovenous connections in the submucosa which* are able to influence directly which blood is delivered to the villi and which is shunted directly into the veins of the portal system Whichever of these mechanisms is at work, it appears reasonably obvious that all mammals possess a mechanism whereby portal blood flow can be regulated in accordance with the needs of digestion Presumably these mechanisms are under nervous control The relationships of the intestinal vessels in the dog are diagrammatically portrayed in

essentially with the views of Gilfillan who states that the portal vein differs fundamentally from veins of the extremities It follows the pattern of visceral veins in general in that it is sparsely equipped with circular fibers, while its longitudinal muscle fibers are well developed. The portal vein, therefore, is constituted primarily of longitudinal fibers interspersed with small amounts of areolar and elastic tissue

The Splanchnic Capillary Bed

muscularis and enter the submucous layer Here a large arterial submucous plexus is found Three sets of arterial capillaries stem from the submucous plexus, one group supplies the muscularis mucosae, while another pierces this layer to form dense capillary networks in the base of the mucosa The third set penetrates the mucosa, almost reaching the surface where it surrounds the orifices of the glands In the stomach and colon, portal blood originates from the superficial capillary network about the glandular elements Soon the capillaries become veins of considerable size which form a large venous plexus between the base of the glands and the muscularis mucosae The veins of the stomach then penetrate the muscularis externa and join large veins draining other portions of the stomach. Interestingly enough, colonic and gastric veins are frequently supplied with valves and have a relatively thick muscular coat

beneath the mucosa The veins arise from the capillary network near the tip of each villus, descend, form a glandular venous plexus, and then pierce the muscularis mucosae to join the veins of the submucous plexus Valves are not present in these veins.

Two important phases of blood transport are ascribed to these particular vascular arrangements If a living villus is observed under the microscope, it is seen to contract rhythmically in its long axis. As it does so, the contents of its capillary bed are forced into the underlying venous plexus The second function ascribed to the intestinal vascular pattern is the sphincter-like action of the arteries as they pierce the muscularis mucosae Closure of these could be relied

ing cells and by reticulum. They constitute a plexiform, three-dimensional system of channels intimately connected with one another by actual and potential passages " The arterioles communicate directly with the capillary ampulla, and on the venous side the pulp spaces converge upon free openings into the venous sinuses These investigators, of course, support the open pattern of splenic circulation as proposed by Mall, Robinson, Foot, and Klemperer

Although this peculiar spongy arrangement for the transfer of arterial inflow to venous outflow has particular significance in the splenomegaly which develops in the presence of portal hypertension, few other important relationships between the splenic blood flow and the portal circulation can be identified As in the case of the pancreas, the splenic vascular bed is simply one source of portal blood As far as is known, the spleen does not elaborate a hormone or other substance directly concerned in the dynamics of the hepatic circulation The only possible relationship rests in the reservoir capacity of the spleen On demand, this organ can deliver from 400 to 1000 ml of blood to the general circulation which, of course, has to pass through the liver on its way to support cardiac output

THE PHYSIOLOGY OF THE EXTRAHEPATIC PORTAL VENOUS SYSTEM

The Portal Venous System in Experimental Animals

The normal physiology of the extrahepatic portal circuits is not complicated, and many of its more salient features have already been discussed in the sections dealing with the intrahepatic circulation Mann's statement that the liver is not the master of its own circulation can be applied with equal appropriateness to the visceral portal bed, blood flow in these channels is subject not only to influences

in the activity of the splanchnic venous bed In lower animals, the story of the hemodynamics of this circulatory system has largely been written in terms of obstruction to its flow and in terms of a variety of venovenous shunts and arteriovenous fistulas which can be fashioned one way or another between the portal system and neighboring vascular structures For many years, the physiology of this system in man was largely deduced from observations made upon animals, of these, of course, many have been shown to be correct, an equal number, however, have been proved incorrect In recent years, renewed surgical interest in treating portal hypertension has opened up this little explored circulatory system to a host

Figure 63 This diagram has been reproduced from Maximow and Bloom's modification of Mall's original plates.

The Pancreas

of the arteries and drain either into the superior mesenteric, the portal, or the splenic veins Because of the extreme vascularity of the islets of Langerhans, it was suspected for many years that these structures might have an endocrine function. In recent years, of course, this has been proved, and it is known that large amounts of insulin enter the blood stream In so far as has been learned, this hormone has neither a direct nor an indirect effect upon the intrahepatic or extrahepatic circulations. Wharton, Berg, and Beck and Berg have carefully delineated the pancreatic circulation, and save for the fact that its venous blood drains directly to the liver, they have not noted a special relationship to the portal circulation The pancreas does not seem to possess any arteriovenous shunts which can eliminate it from the general splanchnic flow. As Knisely, however, has emphasized, the relationship of the pancreatic circulation to the liver has not been extensively studied One feature of the pancreatic circulation noted by Wharton was that though there is generally a close association between the arteries and veins, there are large venous plexuses along the pancreatic ducts which are without arterial counterparts

The Spleen

Unless it be that of the liver, no circulatory bed has been so extensively studied as has that of the spleen. Controversy has centered about whether the spleen presents a "closed vascular system," that is, with a continuous endothelial layer extending from the arteries across the capillary bed to the venous system, or whether its circulation is "open," that is, the blood actually escaping from the arterioles into an open space before being returned to the spleen's venous drainage system Not until the quartz light method of direct observation of living tissue was applied to the spleen were some of the problems concerned at least partially solved McKenzie, A O Whipple and Wintersteiner have probably come nearest to answering completely the many questions involved. They have concluded that the splenic pulp spaces provide the one and only link between the arterial and venous systems in the mammalian spleen. These investigators describe the pulp spaces as being composed of "tortuous, utterly irregular, and inconstant channels lined by fixed and wander-

in Schiff's laboratory in Geneva As was the custom, the professor put this young man to work on portal occlusion Lautenbach returned to Philadelphia some years later and in the "Philadelphia Medical Times" of 1877 published what apparently was a summary

the attention of Nicolai Eck, a young surgeon about to enter the Russian army Eck did not accept, though he does not say why, the conclusions of the Schiff school as reflected in Lautenbach's essay He set about to prove his convictions by devising the famous venovenous shunt which is today so universally referred to as the Eck fistula In 1877 Eck proved beyond doubt that the dog survives sudden portal occlusion quite uneventfully, provided the portal flow of blood is deviated into the systemic circuit This Eck accomplished by a side-to-side anastomosis between the portal vein and the vena cava and then tightly occluding the portal vein liverwards to the fistula Of p.
that a fistula
ascites due tc
went off to the army and, as far as can be determined, the medical world has not heard from him since

So generally unavailable has Eck's original article been to English readers that it was recently translated by Dr Ila N Kovarsky, Secretary of the New York Russian Medical Society, and published in "Surgery, Gynecology, and Obstetrics," Volume 4, page 375, 1953 Although it could have been determined in 1877 that there was very little occult or obscure about death in the dog, cat, and rabbit following sudden occlusion of the portal vein, many intermediate steps were necessary before the final story was written

So definitive were the results obtained in the dog and so important were the impacts of physiological facts derived from dog and cat experiments that the results in these animals were applied unquestioningly to man In spite of good clinical evidence to the contrary, it was believed that man, too, would necessarily die were the portal vein to be occluded suddenly and completely But this is another story to be recorded a few pages hence What have been the most important experiments performed upon the portal circulation to the liver from 1877 until the last few years?

Every few years after the original experiments on total interruption of portal blood flow, laboratory workers in this field reported their results on lesser degrees of interruption of the portal flow Solowieff, attracted, as had been others, to the problem of the etiology of cirrhosis, also undertook to study the effects upon the liver

of investigations, many of which have yielded important contributions to fundamental knowledge concerning the activities of the portal venous bed. Furthermore, the development of methods for estimating hepatic blood flow has provided additional information concerning what actually takes place within the portal vein and its major tributaries.

Although the unique arrangement of the portal circulation (bounded as it is by two capillary beds) early attracted the speculative attention of eminent anatomists, physiologists, and clinicians, interest in portal venous occlusive phenomena originated in a much more practical, important, and as yet unsolved problem—the etiology of cirrhosis of the liver. Beginning along toward the middle of the last century, it was commonly observed at the autopsy table that patients with cirrhosis manifested an accompanying thrombosis of the portal vein. Frerichs, Klebs, Rindfleisch, and others expressed the belief that the thrombosis was directly related to the cirrhosis, while Gintrac, Botkin, and Oré wondered whether or not the cirrhosis might be the result of thrombosis of the portal vein. In 1861 Oré attempted to simulate thrombosis of the portal vein by abruptly ligating this vessel in rabbits. By experiments such as these, Oré was probably the first to discover that one of the usual laboratory animals, the rabbit, died more or less immediately following sudden occlusion of its portal vein. Claude Bernard, two years later, and Schiff, seven years later, repeated Oré's experiments and used the dog rather than the rabbit. Both of these observers noticed that the results were the same, these animals, too, promptly died.

These early experiments, the first of many thousands on the portal circuit, aroused the interest of many contemporary physiologists. The fact most diligently sought for was why these animals died so quickly after sudden and complete portal occlusion. Bernard, occupied as he was so completely with hepatic function, at first did not offer an explanation, but later (1877) he turned his attention to this subject and tentatively suggested that death was due to exsanguination into the venous bed of the gastrointestinal tract. Tappeiner was not satisfied with this explanation, for he believed that he had proved that more blood could be withdrawn from a systemic vein without death than could possibly become impounded in the portal bed. Schiff and his pupils propounded the theory that liver failure was the cause of death in dogs whose portal veins were suddenly occluded. So widespread and great was Schiff's influence that liver failure as the cause of death after portal occlusion enjoyed worldwide acceptance for many years.

In 1874 Lautenbach, a prominent young physician of Philadelphia, repaired to the continent to complete his medical education

due to frank blood loss, that transfusion, although it elevates blood pressure temporarily and postpones the fatal outcome, does not prevent death; that the blocked splanchnic bed cannot perform its usual office in preventing shock

Boyce and his associates agreed generally with Elman and Cole but insisted on retaining the concept that a neurogenic mechanism in part, at least, contributes to the death of these animals In support of this contention, they point to Thole's original experiments in which he proved that section of the vagus nerves prolonged survival but did not avert death In addition to insisting that a neurogenic factor share the responsibility with blood loss, Boyce pointed out that the clotting time lessens appreciably as the experiment progresses toward the death of the animal This phenomenon has not, as far as is known, been explained

In the section upon the relationship of the liver to shock, attention was called to the fact that in spite of the volumes of contradictory evidence, the thought has survived from the earliest experiments to those of the present day that somehow portal occlusion and hepatic function bore a relationship to the state of shock That there is a relationship has been adequately established in recent years, that the connection bears more upon liver parenchymal activity than portal blood or portal blood flow now becomes increasingly obvious

EXPERIMENTS IN MONKEYS The most recent study of portal occlusion has been the review of the entire subject in terms of one of the primates, the Macaca mulatta monkey, and in terms of man These experiments have been performed by the author and his associates while working in the Laboratories of Surgical Research of Dr Frank Glenn at The New York Hospital–Cornell Medical Center Because of frustration in a number of attempts to cure pancreatic cancer because the tumor was found invading the portal vein, experiments were designed to determine whether or not this structure might be resected successfully This thought coincided with the demonstration by Whipple and his associates that man, with or without his liver function impaired by cirrhosis, tolerated well complete diversion of his portal blood into his systemic circulation In the original application for a grant-in-aid from the U S Public Health Service to study this problem, it was proposed that *pancreaticoduodenectomy* be preceded by an end-to-side anastomosis between the superior mesenteric vein and the vena cava I did not, however, want to use dogs in these experiments, for not only did I consider that the vascular physiology in the right upper abdominal quadrant of this animal had been completely worked over, but I also felt that there might be some virtue in studying an animal with anatomical relationships more closely correlated with those of man than are those

of portal occlusion He, too, confirmed the fact that dogs died in four to twenty-two hours after sudden and complete occlusion of the portal vein. Solowieff was dissatisfied with this type of experiment, for he did not believe the animals survived long enough to develop changes in their livers. He, therefore, devised a series of experiments in which the major branches of the portal vein (splenic, superior mesenteric) and finally the portal vein itself were ligated in stages By this technique, Solowieff was able to maintain his animal in apparent good health long enough so that he could observe any changes that might take place in the hepatic parenchyma. By his studies, he concluded that the dog could survive portal occlusion provided it was accomplished in stages Neuhof confirmed these experiments in 1913 During the early 1900's a number of investigators, including Ito and Omi, 1902, and Steenhuis, 1911, reported a series of confusing results relevant to the indispensability of the portal blood flow reaching its destination in the liver. In spite of these, it generally became accepted that the cat, dog, and rabbit could tolerate portal occlusion provided it was accomplished either in several stages or in association with a portacaval shunt. The probable explanation for the many differences of opinion expressed during this period lies in the fact that there is great species variation in response to portal occlusion, either sudden or gradual. There can also be great variation within the same species For instance, some dogs die within thirty to forty minutes after sudden portal occlusion, while others may live on ten to twelve hours. In rare instances, a dog may even survive the experiment

Neuhof, Hallopeau, and Thole (1910–1912) were responsible for adopting Bernard's original theme and applying the concept of shock to the animals succumbing to sudden portal occlusion. In fact, Thole performed the first of a series of experiments which in all likelihood have been repeated thousands upon thousands of times since in laboratories throughout the world. He cannulated the carotid artery of a dog and noted that the systemic arterial pressure fell to one-half its normal value in six to eight minutes, and in most instances the dog died within a few hours The final chapter upon the relationship of shock to death in sudden portal occlusion for the dog and cat was written by Elman and Cole in 1934 These surgeons, employing the Evans blue dye technique for measuring blood volume, proved conclusively that death was due to rapid depletion of the effective circulating blood volume into the splanchnic bed. These experiments were shortly confirmed by Boyce, and it became axiomatic that the cat and dog die after portal occlusion by bleeding to death into their own splanchnic beds Elman and Cole concluded that, in such experiments, the animals present the picture of death

to ten days after operation, this measured repeatedly at levels little if any above the pre-occlusion level This observation together with the poor results obtained in our one-stage pancreatectomy led to the concept of a two-stage operation for the resection of the head of the pancreas, the duodenum, and the portal vein At the first stage, it was proposed that the portal vein be occluded At the second stage, [illegible]

[illegible] of our experiments Incidentally, we all became so engrossed in our studies of portal occlusion that our original plan to perform portacaval shunts was completely side-tracked

At first the two stage operation fared no better than the one-stage, when transfusions were added to our surgical armamentarium, our animals began to survive from several days to several weeks The difficulties in rendering even a trace of good postoperative care to monkeys are immense, and the predictions of the study section of the U S Public Health Service upon how devilish were monkeys and how impracticable their care were confirmed many times Nevertheless, we reached the conclusion that pancreaticoduodenectomy with resection of the portal and superior mesenteric veins was a feasible, though harrowing, operative procedure in the Macaca mulatta monkey The details of all the experiments performed upon the Macaca mulatta monkey are recorded in Appendix 2

The Eck Fistula in the Experimental Animal

The annals of surgical research are replete with remarkable technical accomplishments But probably none is more extraordinary than Nicolai Eck's feat of fashioning successfully an anastomosis between the portal vein and vena cava at a time when antimicrobials were unheard of and vascular surgery had hardly been considered possible Yet in 1877 this obscure Russian army surgeon calmly announced that he had succeeded in diverting all of the portal blood flow directly into the inferior vena cava In this day of direct intima to-intima suture of blood vessels, Eck's original technique may [illegible]

[illegible] favor in some laboratories

Eck's original technique for the anastomosis which now bears his name required that the portal vein and vena cava be sutured together in such fashion that the external surfaces of the two vessels opposed each other over an oval area approximately 3 by 0 5 cm At one end, the sutures were untied and through this aperture Eck

of the dog I chose, therefore, as my experimental animal the Macaca mulatta monkey

The first animal to enter our laboratory was a splendid fellow called Jocko Roger Milnes, a fourth year medical student, and I set about fashioning an anastomosis between Jocko's portal vein and his vena cava However, our best efforts resulted in having to ligate the portal vein Jocko was returned to his cage to await the dismal end which we were all confident *must follow By ten in the evening of* the day of operation, Jocko was obviously recovering from his anesthesia and the next morning he breakfasted heartily. Monkey dealers were harassed far and wide to speed their prize specimens to our laboratories, and in a series of 76 animals, 59 survived sudden and complete portal occlusion Our series grew, and it was terminated in 1951 with an uncorrected operative mortality of 22 per cent, certainly a wholly different picture from that seen in commoner laboratory animals subjected to the same type of experiment

At weekly intervals the hemodynamics of the portal circulation of the monkey was studied by means of portal venography and manometry As a result of these carefully controlled experiments, the explanation for the survival of this primate became obvious; as the portal pressure rose after portal occlusion, portasystemic collaterals opened widely enough to permit sufficient blood to flow into

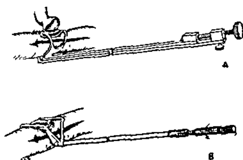
with a sufficient number of preformed portacaval shunts. (See Appendix 1 for complete details of these experiments.)

All engaged in the experiments more or less simultaneously reached the conclusion that as this primate tolerated portal occlusion so well, this vessel could perhaps be resected together with the pancreas and duodenum Accordingly, 6 monkeys were subjected to a one-stage pancreaticoduodenectomy with resection of the portal vein In 5 animals, the operation could barely be completed before the animals died, obviously the victims of hemorrhagic shock. After occlusion of the portal vein, blood oozed uncontrollably from every conceivable capillary which had been divided within the field of operation One animal survived this one-stage operation for twenty-four hours, it was tentatively postulated that this monkey possessed a sufficient number of portasystemic connections to permit his survival for this period

An observation of great importance which was made during the course of the weekly portal venography and manometry to which these animals were subjected concerned the fact that the initially produced portal hypertension rapidly subsided By the end of seven

Eck and the reverse Eck fistula in animals, it has not proved suitable in man

A few years after the development of the cutting suture technique, both Jerusalem and Jeger developed small, light, narrow-bladed clamps which, when applied appropriately, provided a technique whereby the portal vein and vena cava could be sutured together directly without seriously compromising blood flow in either vessel Although clamps for the direct and unobstructive suture of blood vessels have undergone many revisions since their introduction by these two investigators, the general principles involved have proved sound and are in extensive use today Clamps allowing free manipu-



lation of the walls of the vena cava for suture, yet simultaneously permitting blood to flow largely unimpeded through this vessel itself, are available today in a number of different designs The two in common use today are those designed by Potts and by Large (Fig 64 A and B) The Potts clamp, although a very useful instrument requires the freeing from its bed of a long segment of vena

two clamps were required, one applied to the vena cava and one to the portal vein In fashioning a shunt for portal hypertension, only the caval clamp is required because the collateral circulation is so great that the portal vein can be completely occluded for long periods of time without hazard

Another important feature of venovenous anastomosis was expounded many years ago by Franke This investigator, impressed by the unfortunate tendency of venous shunts to close, described

introduced a small pair of scissors tipped with guide wires. With these the walls of the *opposed vessels were slit, thereby connecting* the portal and systemic circulations. The scissors were then withdrawn, and the point of exit closed by tying the sutures which had already been placed. After ligating the portal vein liverward to the anastomosis, all of the portal blood flowed into the vena cava. One of the features of Eck's original operation was that blood flowed *normally in both the portal vein and the vena cava until the portal* ligature suddenly diverted the entire portal stream into the vena

siderable amounts was allowed to escape into the systemic circulation

In 1882 Stolnikow adopted Eck's technique in its entirety and reported excellent immediate results and many long-term survivals Pavlov, and a number of years later Guleke, also became interested in what was rapidly becoming known as the Eck fistula dog By improving greatly upon Eck's scissors, they were able to cut through *the walls of the two veins with greater certainty and less trauma.* Both of these early investigators consistently reported successful

from the techniques employed successfully by the earlier investigators *Instead of fashioning the anastomosis in the side-to-side position,* he divided the portal vein obliquely and sutured the splanchnic end to a slit in the anterior wall of the vena cava. Tansini reported that his dogs survived in good health

Markowitz has expressed the belief that the modern era in Eck fistulization was introduced by Fischler and Schroeder. Although Eck's initial steps were followed, a cutting suture of silk was employed instead of scissors to connect the two vessels The stimulus to the development of this technique lay in the desire of these men to avoid even the slightest compression of either vessel during the course of the procedure They believed this to be important "not only because of the congestion which is connected with it [i.e. even temporarily occluding either vessel] but mainly because of the injury which is associated with ligating or clamping vessels which may lead to secondary alterations or injuries" By their cutting suture technique they believed they avoided all of these difficulties. So attractive did this technique prove that it was practiced for many years by F. C Mann, described again by Fishback, and more recently still by Markowitz. In spite of its extensive use for both the

rated in the kidney after partial constriction of the renal artery As far as could be determined, this type of hypertension was not modified by passing renal blood directly through the liver by means of a reverse Eck fistula (Child 1936)

J Sweet in 1923 believed he had improved upon the cutting suture when he replaced this by a wire which, when heated by an electric current, successfully cauterized its way through the vessel walls. Perhaps the most recent modification of the portacaval circulation is its transposition by means of direct suture (see Fig 57, p 144) As developed in our laboratory, this animal preparation was devised to study hepatic regeneration and consists essentially in diverting the caval blood through the liver and the portal blood into the vena cava These experiments are outlined fully in Appendix 6 Whether or not this operation will ever have any application in man is quite unknown From an entirely theoretical point of view, it is possible that it might be found to have some useful application It would obviously decompress the portal circuit and at the same time supply additional amounts of venous blood to the liver

Eck, in his original article, reported that the few dogs that survived appeared to him to be normal in every respect So convinced was Eck of their good health that he did not hesitate to suggest that the operation be used in patients with ascites When, however, Pavlov became interested in these experimental preparations and observed a large series of dogs over a long period of time he became convinced that his animals were not entirely normal A repeated observation was that a certain small number of his dogs appeared quite unable to eat meat without manifesting signs of a severe systemic intoxication The most important features of this state were convulsions, periods of depression, ataxic gaits, catalepsy, and occasionally blindness This state was also observed in a number of other laboratory animals with Eck fistulas and became a point of considerable discussion Little of a specific nature concerning it has ever been established save that it need not necessarily appear Even today the question of the normality of the Eck fistula animal is controversial The most persistent explanation for this state is that the liver exercises some vague sort of direct censorship over products of digestion and other equally vague but noxious substances originating in the gastrointestinal tract So convinced were early investigators of the reality of colonic toxins that they delighted in referring to the gastrointestinal tract as the body's cesspool Several years ago, Markowitz stated that the experience of the Mayo Clinic warranted the generality that "dogs with an Eck fistula enjoy reasonably good health if meat is not given them and especially if their diet consists

a technique whereby he hoped to avoid this complication After preparing a section of vena cava 4 cm in length, its lumen was entered "by way of an oval hole corresponding in size to the diameter of the portal vein " In suturing the portal vein to the vena cava today, excision of a button of caval wall is considered an essential part of the operation whether the anastomosis be performed in the end-to-side or side-to-side position

Another variation upon the direct suture technique employs a glass or metal prosthesis Credit for devising such a technique must be given to Quierolo who used a short length of glass tubing over which he everted the cut end of the portal vein. This then was inserted into the vena cava and held in place by a purse-string suture His technique has been employed successfully in many different animal experiments and applied to man by Blakemore and Lord early in their experience with portacaval shunts These latter investigators employed small vitallium tubes on the basis that this metal was least apt to produce tissue reaction Unfortunately, tissue reaction did occur, and the technique was abandoned by them within a few years in favor of direct suture

In 1912 Franke devised another type of Eck fistula in which he omitted the occlusive ligature upon the portal vein and to which he referred as a "false Eck fistula " He expressed some concern as to

ganism as a whole It is this "false Eck fistula" which finds favor in the hands of those surgeons today who believe that in portal decompression an effort should be made to allow at least some portal blood to pass through the liver This operation currently is referred to as a side-to-side anastomosis in contrast to one of the end-to-side variety It should not be confused with the original Eck fistula which, although performed in the side-to-side position, carried with it ligation of the portal vein above the site of anastomosis. In effect, then, Eck's side-to-side anastomosis is functionally an end-to-side shunt

Many others interested in hepatic physiology have worked from time to time with the Eck fistula and in doing so have devised an almost endless variety of innovations. Ludwig Mayer is credited with fashioning the first "reverse Eck fistula" which, of course, involves ligating the vena cava cephalad to the anastomosis and

been ligated than collaterals begin to form and within a very short time by-pass the point of obstruction Almost within a matter of weeks normal or near normal hepatic flow has been reestablished Furthermore, in the four or five patients in whom the portal vein has been resected for cancer there is little evidence that any state resembling the meat intoxication syndrome appears Either man's reaction is comparable to that of the monkey or other as yet undetected factors are present At the moment, it appears likely that as these various problems are studied further they may be resolved around certain peculiarities inherent in the hepatic physiology of the dog

The Portal Venous System in Man, Including Banti's Disease

Precise knowledge of the physiology of the portal venous system in man has lagged far behind that which has been accumulated for experimental animals The reason for this delay is obvious, it is not permissible to experiment deliberately upon man if the risk to life and health is great Because man's portal venous system is generally unavailable for study except by exploratory laparotomy, physicians and surgeons have had, until recently, to depend upon indirect sources for their basic information concerning the physiology of human portal venous circuits

Pathologists have been able to supply a certain number of adynamic facts deduced from postmortem examination of both normal and abnormal portal veins Correlation of autopsy findings with clinical information acquired antemortem has provided a fund of information which has generally been found valid Many of the beliefs concerning portal hemodynamics have, however, been based primarily upon information acquired in the study of laboratory animals On relatively rare occasions, surgeons have been able to contribute a few facts of a more dynamic nature from observations made at the operating table The import of these indirect observations and deductions led to the commonly held opinion that the portal venous system must not be tampered with, if it were, either accidentally or purposefully, man, even as the cat and dog, would promptly die

Recently, a number of improvements in investigative techniques have been introduced which permit study of the portal venous system without undue risk and with greater accuracy than has been possible in the past Monkeys have been added to the list of available experimental animals, and it has been shown that their portal hemodynamics correspond closely to those in man. Portal venography (see Chap 14) has been developed to a point where it is useful

of dog biscuit, milk and syrup " In addition, Markowitz expressed the conviction that following an Eck fistula, the liver undergoes atrophy "which is well marked at eight weeks"; at this time the liver is "one third its original size " This and the fact that hepatic tissue does not regenerate completely in the absence of portal blood appear to be well established today. In addition to these facts, G H. Whip-

fest certain important

nufacture hemoglobin

Johnston have expressed the belief that meat intoxication may in reality be potassium intoxication Hallett and his associates have been able to prove a 50 per cent reduction in hepatic oxygen consumption in the presence of an Eck fistula In spite of this, glucose production was normal These investigators took especial care to point out that the postoperative course in all of their animals was remarkably uneventful.

In a recent article upon this subject, Markowitz emphasizes that, contrary to his beliefs of a few years past, most of his animals with Eck fistulas enjoy remarkably good health. So important did Markowitz consider his present opinion that he felt called upon to try to explain the convulsions and other signs of ill health which he had previously reported In attempting this, Markowitz admitted that he had little to call upon other than speculation Nevertheless, he felt justified in pointing out that in many of the original experiments the operation was time-consuming and traumatic. These factors may have led to such extensive fibrosis at the porta hepatis that the he-

hepatic decompensation and coma In many respects the "meat intoxication syndrome" resembles the state of these animals in hepatic decompensation Whether this analogy be correct or not will perhaps never be proved, but for the time being at least, it seems a more logical hypothesis than any heretofore proposed

In our own laboratory where Macaca mulatta monkeys have been deprived of all portal hepatic blood flow by sudden and complete occlusion of the portal vein, it has been impossible to detect in them any manifestations of a clinical state comparable with the meat intoxication syndrome described in dogs It is true, of course, that these monkeys will not eat meat in any appreciable quantities In addition, it is also true that in them no sooner has the portal vein

circuit without traversing the liver De Jong, Reddinguis, Thole, Charpy, and Thomson all worked out in elaborate detail the innumerable pathways by which portal blood could, if called upon to do so, escape into the systemic venous circuits Not only was the existence of these channels demonstrated in normal man, but it was well recognized in patients with cirrhosis In them they were elaborated into the many collateral pathways too well recognized today to warrant repetition in this volume The picture, then, of splanchnic congestion and developing collaterals contributed two physiological facts of major importance in man that the portal venous system is not closed, and that if portal flow is progressively compromised man survives indefinitely

Early knowledge of the hemodynamics of portal blood flow cannot be left without mention of the work several French scientists undertook about 1900 Led by Gilbert and Weil, and Villaret, and Pichancourt, investigators became interested in measuring the pressure under which ascites collected in the peritoneal cavity They found the pressure elevated to high degrees and concluded that in the portal vein it must also be elevated a like degree If it were not, these vessels would collapse as soon as any appreciable amounts of ascitic fluid collected This phenomenon they designated portal hypertension To the static observations of the older investigators, the French school added a more dynamic concept, the splanchnic vessels in cirrhosis not only were congested, but in addition the *pressure within them must obviously have been elevated appreciably*

Another obstruction to portal blood flow which over the years has contributed extensively to the fund of physiological information concerning the portal circulation in man was variously referred to as congenital stricture, cavernomatous transformation, or thrombosis, Here these will be referred to collectively as chronic obstruction of the portal vein and the innumerable controversies as to its etiology will be disregarded In any number of reported cases, the onset of the obstruction was well correlated with clinical manifestations and often confirmed by postmortem examination By combining these several observations, a comprehensive picture of the effects *of portal obstruction in man was constructed* Before elaborating these concepts it must be pointed out that occlusion of the portal vein by a bland thrombotic process is more important in terms of physiological interpretation than when the obstructing process is septic in origin In the latter instance the perpetrating factors, acute appendicitis, portal pylephlebitis, peritonitis and the like, all too often obscure the picture of pure portal obstruction by superimposing upon it the signs and symptoms of an acute septic disease Dis-

in studying the portal system dynamically and antemortem. The greatest stimulus to further investigations of the normal and abnor-

supportive therapy, have contributed importantly to the elaboration of basic information concerning normal and abnormal portal physiology.

As scientific medicine and surgery were being developed, the clinical features, both antemortem and postmortem, of patients with cirrhosis of the liver contributed heavily to the early accumulation of myths and facts concerning the portal circulation. One of the earliest observations, of course, was that cirrhosis was often associated with ascites At the autopsy table patients with this disease were routinely observed to present greater or lesser degrees of dilatation of the veins of the splanchnic bed This fact was correctly interpreted as due to impaired blood flow through the liver and uniformly referred to as "congestion" To this congestion, of course, was ascribed the formation of ascites For many years it was considered self-evident that whenever portal congestion occurred, ascites was formed simply by transudation across the venous capillary walls and the peritoneum So direct was this relationship considered that it led Eck to propose that his fistula might be useful in preventing this troublesome collection of fluid within the peritoneal cavity. Today, of course, it is known that the formation of ascites is a far more complicated process

Early in the study of patients with cirrhosis, it was observed that the portal vein was often the site of extensive thrombus formation As mentioned earlier, this observation led Oré and Solowieff to perform experiments on animals designed to determine whether cirrhosis was not in itself due to impaired portal blood flow. Space does not permit discussion of all the controversies on exactly this point that went on during the latter part of the last century. Although most investigators admitted that the evidence was equivocal, the consensus was that liver function was seriously impaired if the flow of portal blood was interrupted

It was learned many years ago from the study of patients with cirrhosis that the portal venous system in man was not closed as it apparently was in lower animals This fact is clearly reflected in the extensive writings of R Josselin de Jong who pointed out in 1912 that the portal system possesses many anastomotic channels with the systemic venous system Through these the portal blood in greater or lesser amounts finds direct access to the major venous

laterals All authors agreed that the spleen was enlarged and that a large collateral circulation was present comparable in extent to that seen in impairment of portal blood flow due to cirrhosis of the liver It was clearly recognized that esophagogastric varices were often present, and that these were frequently the source of a severe hemorrhage was also appreciated Most authors agreed that the liver was normal but that it was so by virtue of some blood reaching it through

[illegible]

it appeared Its absence, however, produced considerable controversy, but was usually explained away with the statement that sufficient collaterals had developed to drain effectively the splanchnic venous congestion

At this point should be added another type of portal occlusion This is referred to by Himsworth as "acute and complete occlusion of a normal vessel (portal vein) " This he states is most commonly seen after splenectomy and in patients with polycythemia vera Himsworth states that such a catastrophe is characterized by the rapid accumulation of ascites, the appearance of melena, colicky abdominal pain, and ileus The spleen, if present, may enlarge rapidly Death follows within a few days In studying the cases of acute portal thrombosis which have been reported, it appears evident that this train of events may take place in man although the picture is certainly not that appearing after ligature of the portal vein This apparent conflict can be resolved only by assuming that in patients with acute thrombosis referred to by Himsworth the obstruction could not have been sharply limited to the mid-portion of the portal vein as in the case of ligature It undoubtedly must have extended further to have blocked successfully the splenic, inferior mesenteric, and superior mesenteric Whereas simple and sharply delineated occlusion of the portal vein does not result in immediate death, any such extensive thrombotic process as has been postulated to account for the type of case described by Himsworth would probably result in the rapid death of the patient

To observations such as these, a few more have been added by surgeons as a result of their experiences at the operating table In 1913 Burdenko reported a patient whose porta hepatis had been so badly injured that the portal vein had to be compromised This was followed within a few moments by a severe fall in blood pressure and death In another patient, the portal vein had to be ligated in the course of dissecting out a large number of upper abdominal

cussion will be limited, therefore, to those patients in whom the process was presumed to be bland in origin.

Heller was probably the first to describe clearly a patient with a thrombosed portal vein whose liver was normal, whose spleen was enlarged, and who presented definite evidence of varicosities of the coronary venous system In this patient, there was no evidence of ascites Pick was largely responsible for the introduction of the term cavernoma of the portal vein, and on the basis of his observations he devised the concept of a hepatofugal and hepatopedal circulation, the former for decompressing the congested splanchnic bed, the latter for supporting liver function In 1914 Enderlen, Hotz and Magnus-Alsleben published an extraordinarily comprehensive review of portal venous occlusion They outlined the history of a woman who fell from a wagon and, although there was no outward sign of injury, she soon noticed severe upper abdominal pain which persisted. *She was ill without specific complaints for the better part* of a month, and just as she was beginning to improve she developed hematemesis and tarry stools An exploratory celiotomy for presumed gastric ulcer showed the spleen enlarged but the liver normal. There was no evidence of ulcer. This patient continued to bleed into the gastrointestinal tract and died six months after the presumed onset of her portal thrombosis At autopsy the portal vein was completely thrombosed

In contrast to this patient whose primary manifestation of portal thrombosis was gastrointestinal hemorrhage is a case reported by Falkenberg in 1928 This patient, a man aged thirty-three, suddenly became weak and for several days vomited blood and passed tarry stools Following this episode, he was well for eighteen months but then began to develop ascites This continued and required many paracenteses and posed so much of a problem that thirty months after the onset of his illness, a Talma operation was attempted. He died on the sixteenth day after operation The autopsy revealed that the portal vein was constricted and dorsally flexed by a small cavernomatous mass of tissue lying in its wall about 6 cm from the porta hepatis The liver was normal, the spleen and pancreas were enlarged and fibrotic, and the hepatic artery hyperplastic There were esophageal varices

Cases such as these can be collected almost without limit from the medical literature from 1900–1930 * They typify the medical thinking during this period on the effects of bland portal thrombosis which progressed slowly enough to permit the development of col-

* Ehrenteil, Gross, Gruber, Kaspar, Koebrich, Kuhr, Loeb, Palmedo, Risel, Umbreit, Versé, Emmerich, Josselin de Jong

laterals. All authors agreed that the spleen was enlarged and that a large collateral circulation was present comparable in extent to that seen in impairment of portal blood flow due to cirrhosis of the liver It was clearly recognized that esophagogastric varices were often present, and that these were frequently the source of a severe hemorrhage was also appreciated Most authors agreed that the liver was normal but that it was so by virtue of some blood reaching it through collateral channels by-passing the site of obstruction (the hepatopedal circulation of Pick) In regard to whether or not ascites developed, there appeared to be considerable question and confusion Obviously, ascites was expected and little comment was made when it appeared Its absence, however, produced considerable controversy, but was usually explained away with the statement that sufficient collaterals had developed to drain effectively the splanchnic venous congestion

At this point should be added another type of portal occlusion This is referred to by Himsworth as "acute and complete occlusion of a normal vessel (portal vein) " This he states is most commonly seen after splenectomy and in patients with polycythemia vera Himsworth states that such a catastrophe is characterized by the rapid accumulation of ascites, the appearance of melena, colicky abdominal pain, and ileus The spleen, if present, may enlarge rapidly Death follows within a few days In studying the cases of acute portal thrombosis which have been reported, it appears evident that this train of events may take place in man although the picture is certainly not that appearing after ligature of the portal vein This apparent conflict can be resolved only by assuming that in patients with acute thrombosis referred to by Himsworth the obstruction could not have been sharply limited to the mid-portion of the portal vein as in the case of ligature It undoubtedly must have extended further to have blocked successfully the splenic, inferior mesenteric, and superior mesenteric Whereas simple and sharply delineated occlusion of the portal vein does not result in immediate death, any such extensive thrombotic process as has been postulated to account for the type of case described by Himsworth would probably result in the rapid death of the patient

To observations such as these, a few more have been added by surgeons as a result of their experiences at the operating table In 1913 Burdenko reported a patient whose porta hepatis had been so badly injured that the portal vein had to be compromised This was followed within a few moments by a severe fall in blood pressure and death In another patient, the portal vein had to be ligated in the course of dissecting out a large number of upper abdominal

lymph nodes This patient survived, and Burdenko credits survival to the existence of chronic compression of the portal vein for a long enough period to permit the development of collaterals. Bernstein reported a patient in whom resection of the portal vein in connection with removal of a large echinococcus cyst was quite uneventful. In 1926 Colp became interested in trying to save the lives of patients with ascending pylephlebitis secondary to acute appendicitis and generalized peritonitis. In several patients Colp deliberately ligated the portal vein, and though these patients all died within a few days, Colp expressed the opinion that the immediate cause of death was probably their primary disease rather than the portal occlusion. In 1945 Brunschwig reported a patient whose portal vein had to be occluded during the course of pancreatectomy. Although this patient died, death did not seem to be due to the portal occlusion. A year later, Andrus similarly occluded the portal vein in a patient operated upon at The New York Hospital, this patient too died, but at postmortem the gastrointestinal tract appeared to be normal.

On this wealth of material collected over a half century has been based the general consensus as to what happened when the portal [illegible]

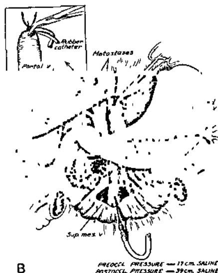
die, although very recently two cases have been reported in which it seemed unlikely that death was due to portal occlusion In regard [illegible]

developed varices and bled is well documented. That in a few others ascites occurred in the absence of liver disease also appears apparent from a review of all the recorded cases.

EXPERIMENTAL PORTAL OCCLUSION IN MAN. The most recent contributions to knowledge concerning occlusion of the portal vein in man are those of the senior author of this monograph and his associates After proving that the Macaca mulatta monkey survived sudden portal occlusion quite uneventfully, a suitable human patient on whom to try the procedure was sought This objective soon materialized in two patients with inoperable carcinoma of the stomach. In both of these patients, the criteria for inoperability were peritoneal implants without evidence of significant hepatic metastases or signs of preexisting portal obstruction In both of these initial experimental subjects, the portal vein was deliberately ligated at the porta hepatis. In both there was a transient fall in systemic arterial blood pressure lasting about ten to twenty minutes and amounting to about 20 to 30 mm of mercury Just as in the monkey, the portal

pressure rose precipitously from a pre-occlusion level of 10 and 12 cm respectively to 35 to 40 cm of saline The upper small intestine and stomach became dusky and engorged with blood and the spleen became tense Except for these intra-abdominal changes, the patients' normal physiological processes appeared undisturbed They left the operating table in good condition and recovered as though





B Sudden and complete occlusion of the portal vein in a patient with a large carcinoma of the head of the pancreas Portal pressure rose precipitously from 17 to 39 cm of saline

from any simple exploratory celiotomy An immediate post-occlusion portal venogram in man is shown in Figure 65A In Table 3 are outlined preoperative and postoperative liver function studies in this comparable patient In Chapter 15 is detailed the pertinent data on an additional five patients subjected to sudden and complete occlusion of the portal vein as a first stage operation in preparation for a radical pancreatectomy with resection of the portal vein

By these deliberate experiments upon man (Fig 65B), it has been shown that 7 human patients have survived sudden and complete interruption of their portal circulation. This, of course, does

TABLE 3

LIVER FUNCTION TESTS PERFORMED AFTER SUDDEN AND COMPLETE OCCLUSION OF THE PORTAL VEIN
(Cf Fig 65A)

Operation Ligation of Portal Vein

A. L. #368488 Female Age 59 Diagnosis Inoperable Ca Stomach (Peritoneal Metastases)

	HGB RBC WBC	PROTHROMBIN UNDIL DIL ST'D	UREA	SUGAR	PROTEIN TOTAL A/G RATIO	PHOS	ICT IND	CHOL CHOL E	BSP	ALK PHOS	THYMOL TURB	CEPH FLOC
Pre-Op	12 6 3 8 6 9	15 2 39 6 40 4	14		6 9 5 4/1 5							
Lig P V			13	218								
Post-Op 1	11 1 3 6		12	89	6 6 5 0/1 6	3 4	5		3 4	3 1	1	
Post-Op 2	10 8 3 4	14 4 32 9 37 0	9	103	6 7 4 9/1 8	3 5	4			2 4	1	6
Post-Op 3			11	104	6 5 4 9/1 6	3 9	4	268 195 5		2 6	0	6
Post-Op 6				97		Bilirubin 0 8					1	
Post-Op 10		13 8 35 6 37 5	10		5 9 4 2/1.7				2 8	3 1		6

This patient presented herself with inoperable gastric cancer but without hepatic or periportal lymph node metastases She survived sudden portal occlusion quite uneventfully, although she did die within a few months from her gastric neoplasm Significant changes in hepatic function cannot be detected

not mean that all patients can be counted upon to tolerate this procedure Reasoning from the series of experiments performed upon the monkeys, it would appear reasonable to anticipate a 10 to 20 per cent mortality It should, however, be possible to avoid any immediate deaths if permanent ligature is preceded by a period of temporary occlusion of the portal vein and if at the same time the systemic arterial pressure is closely followed Should the pressure fail to return to pre-occlusion levels within twenty to thirty minutes after occlusion, the operator should conclude that this particular patient cannot tolerate ligature of his portal vein Such a train of circumstances would have to be interpreted as one of the criteria of inoperability were the occlusion necessary as a preliminary step in a radical resection of the portal vein by a two-stage operation

It remains to attempt to correlate these experiments with recorded cases in which sudden occlusion of the portal vein has terminated fatally Most of these have been reported in connection with presumed thrombosis of the portal vein Here, of course, it has not been possible to know just how extensive was the thrombosis Should this involve the portal, superior mesenteric, and splenic vein, it is possible that the patient's reaction would be like that of the dog and cat In other words, such an extensive occlusion might effectively convert the portal bed from an open to a closed circuit Under such circumstances the patient's effective circulating blood would probably be trapped in his splanchnic bed It is almost certain that if man is deprived of circulation through his coronary, inferior mesenteric, splenic, and superior mesenteric veins, he will die The validity of this hypothesis was well borne out in the case of M F, in whom a one-stage resection of the pancreas, duodenum, and portal vein was completed This patient, however, died in shock (in spite of adequate blood replacement) after about eighteen hours In all respects this patient's normal cardiovascular physiology was disturbed in a fashion comparable to that of a patient suffering an extensive thrombosis of the portal-splenic-superior mesenteric junction

In sharp contradistinction to this patient is E C This young woman required a subtotal pancreatectomy for fibrocalcific pancreatitis During the course of operation the portal vein was so extensively torn that it had to be resected as shown in Figure 66 Immediately after resection of the portal vein, the pressure in the superior mesenteric vein was only 24 cm of saline It was fortunate of course that the inferior mesenteric vein in this patient entered the superior mesenteric vein and served to decompress her splanchnic venous bed by way of her pelvic collaterals She survived her operative procedure quite uneventfully, and it is doubtful whether she

will ever develop esophageal varices because her splenic circulation has been resected and her coronary flow persists unimpeded.

OCCLUSION OF SUPERIOR MESENTERIC AND SPLENIC VEINS It is obvious that the preceding paragraphs have dealt primarily with obstruction to portal blood flow without regard to superior mesenteric and splenic veins as distinct and separate entities. As the available information upon these two vessels is reviewed, it is difficult to differentiate occlusions of either one or the other or both as impor-

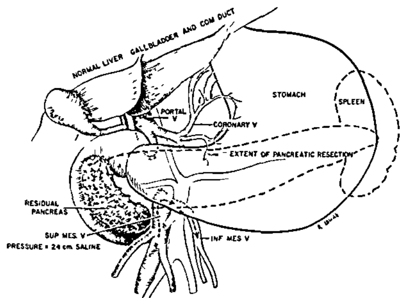


Fig. 66 E C, N
During the course
the portal vein was
placed inferior mesenteric vein conveniently provided adequate portal decompression Because of normal coronary venous drainage, it would seem unlikely that this patient would ever develop esophageal varices

tant either clinically or physiologically It is impossible save in one or two instances to find their occlusion separable from that of the portal vein

In so far as the superior mesenteric vein and its lesser branches are concerned, only two relevant facts are available. One concerns thrombosis, either bland or septic, of the superior mesenteric vein. This subject has recently been extensively reviewed by North and Wollerman who recognized that mesenteric venous occlusion due to phlebitis can occur spontaneously in otherwise healthy individuals. This condition, first recognized in 1866 by Sir James Paget, has been reported under a variety of names and has always proved a

most perplexing clinical entity. Occasionally, it is associated with peripheral thrombophlebitis and occasionally appears to involve the mesenteric veins primarily. A major vessel may be involved and the picture of intestinal obstruction, infection, and peritonitis quickly appears, or lesser segments of intestinal veins may thrombose and give rise to abdominal pain and signs of partial intestinal obstruction with spontaneous recovery

Another and by far the commonest type of splanchnic venous thrombophlebitis occurs secondary to trauma, surgical operations, heart failure, and polycythemia The extent and nature of the phlebitic process, of course, determine the seriousness of the sequelae, it may lead to gangrene of a segment of gut, and not infrequently has been shown to be the source of pulmonary emboli

Recently Madden, intrigued by the possibility of treating cirrhosis of the liver by venous occlusion, tied off the superior mesenteric vein in an effort to relieve the liver of some of the burden of its blood flow This patient rather promptly developed extensive splanchnic infarction and died It seems reasonable to postulate, therefore, that occlusion of a previously unobstructed superior mesenteric vein is not tolerated at all well by man Depending upon its extent, a major thrombosis of the mesenteric vessels becomes a serious catastrophe requiring immediate surgical intervention

BANTI'S DISEASE Before leaving the subject of thrombosis of the portal-splenic-superior mesenteric complex of veins, the subject of Banti's disease, splenic anemia, and congestive splenomegaly must be considered. The term splenic anemia was presumably first used in 1866 by Gretsel to describe a child with splenomegaly and an anemia [illegible]
tosis H [illegible]
dition p[illegible]
of a long series of papers which led to the common use of his name in connection with the syndrome as it is known today Although it was recognized earlier in the nineteenth century that thrombosis of the portal vein in the absence of cirrhosis of the liver led to enlargement of the spleen, splanchnic venous congestion, esophageal varices, and hemorrhage, these observations were not generally correlated with the picture of splenomegaly and anemia described by *Guido Banti In his first article on this subject, Banti* cited the case of a young girl who at the age of sixteen developed an enlarging spleen and progressive anemia In his initial formulation of this case, Banti pointed out that two years after *the onset of her disease* she was "stricken with hepatic cirrhosis," but he emphasized that this was not Laennec's cirrhosis in its usual form His original idea was that the splenomegaly was primary and that this was somehow

related to the development of the patient's cirrhosis A few years later (1894), Banti published an article entitled "Splenomegaly with Hepatic Cirrhosis" in which he added three cases to his first one All of these individuals had been followed by him for a long time and had ultimately come to autopsy.

In his second publication, Banti outlined the criteria for a diagnosis of the disease which for years has borne his name and which has given rise to so much clinical confusion He described his patients as "young adults," although actually the four cases constituting the basis for his report ranged in age from fifteen to fifty-four years Banti considered the absence of the usual etiological factors generally associated with Laennec's cirrhosis to be of great importance In none of his cases was he able to elicit a history of alcoholism, dietary deficiency, infection, poisons, or toxins. He believed that the disease ran a long progressive course, the features of which were anemia and splenomegaly These antedated the appearance of cirrhosis and ascites During a period lasting from one to four years, his patients had been relatively asymptomatic General weakness, easy fatigability, and left upper quadrant discomfort due to the enlarged spleen were often their only complaints This initial period then often merged almost imperceptibly into the second phase of the disease which was characterized by progression of the anemia, digestive disturbances, evidence of early liver failure, and oliguria He called this the intermediate phase It characteristically lasted only a few months, and then rapidly progressed to the third or terminal phase of the disease This was characterized by ascites and death in liver failure Interestingly enough, in none of his many papers on this subject does Banti mention hematemesis as a prominent feature, rather he stresses liver failure as the cause of death. Although Banti repeatedly pointed out that the etiology of this disease was unknown, he expressed the belief that the primary site of involvement was the spleen Furthermore, he surmised that the periarterial fibrosis in the spleen which is commonly referred to as fibroadema of the malpighian bodies was distinctive and pathognomonic

As others, primarily interested in splenic enlargement, began to study patients manifesting this phenomenon, a number of reports appeared roughly paralleling Banti's For instance in 1900, Osler reviewed his experiences with fifteen patients whose spleens were enlarged and who had a definite anemia Osler credited Giesinger with having coined the term "splenic anemia." He pointed out that he had had no personal experience with the disease described by Banti. In addition to the splenomegaly and anemia, Osler recog-

nized that generalized lymphadenopathy was not present and that esophageal hemorrhage was occasionally an additional feature of the condition Osler concluded from his study of this group of patients that until a specific etiology could be found, their disease would have to be designated as a syndrome characterized by enlargement of the spleen and anemia without lymphatic enlargement

As interest began to be focused upon this clinical picture, a num-

[illegible]

mary splenomegaly and septic thrombosis of the splenic and portal veins Edens in 1908 for the first time postulated that portal thrombosis occasionally became associated with a clinical picture similar to that described by Banti Simultaneously, Cauchois expressed the belief that Banti's was not primarily a disease of the spleen but that portasplenic thrombosis was directly responsible for its development Warthin in 1910 and Eppinger a few years later again emphasized the great similarity between Banti's disease and the splenomegaly developing secondary to chronic thrombosis of the splenic vein Over the next twenty years, a number of men, chiefly Hart, Klemperer, and Janabee, stressed repeatedly that in reality Banti's disease was not a disease at all but a syndrome developing secondary to obstruction of the portal or splenic veins

McMichael in 1934 and Rousselot in 1936 deserve the greatest credit for finally clarifying the relationship between portasplenic venous thrombosis and the clinical picture variously designated as splenic anemia, congestive splenomegaly, and Banti's disease McMichael reviewed congestive splenomegaly from the pathological viewpoint under the heading of hepatolienal fibrosis He took his lead from the pathological changes occurring in the lung secondary to increased pulmonary arterial pressure, and decided that a comparable condition might exist in the spleen wherever pressure was elevated in the portal venous system Furthermore, he described periarterial fibrosis and dilated venous sinuses in the spleen whenever an acute inflammatory disease of the liver was present He believed that the splenic abnormalities were intensified but not necessarily caused by increased portal pressure So convinced was McMichael of the correctness of his hypothesis that he took the microscopic sections of the spleen, which he had studied, to Aschoff for review Aschoff, who had seen Banti's studies, agreed with McMichael that the two lesions were identical By this time, then, it can be accepted that the fibroadenia of Banti had been associated directly with increased portal pressure

The next step was taken by Rousselot in 1936 and by Thompson, Caughy, Whipple and Rousselot in 1937. At the operating table they measured the pressure in the splenic vein of a great number of patients with splenomegaly and found marked increases when- [illegible] of Banti's disease In addition, they had all had hematemesis, and in each the liver was normal He showed conclusively that the clinical picture in all was due to portasplenic obstruction, usually caused by chronic thrombosis After nearly fifty years, then, the etiological factor involved in at least one group of patients characteristically fulfilling Banti's criteria has been clarified Whether in some of the patients coming under this general heading it will ultimately be shown that the disease was initiated by a factor other than portal hypertension is a question as yet unanswered. Ravenna presents good evidence that so-called congestive splenomegaly can exist without venous obstruction In children there also seems to exist a type of congestive splenomegaly which Hora has shown to be unassociated with obstruction to splenic blood flow. These divergent opinions have yet to be reconciled with the bulk of current evidence which favors the opinion that the majority of patients have developed Banti's syndrome secondary to portasplenic thrombosis

Out of this wealth of clinical, pathological, and surgical investigation has come the single fact that in man, chronic obstruction of the portal and splenic vein by thrombosis leads to enlargement of the spleen, the formation of esophagogastric varices, anemia, and leukopenia It seems strange that this picture cannot be reproduced successfully in the experimental animal by operative occlusion of the splenic vein. Simple ligation of the splenic vein in common laboratory animals leads to little more than splenic atrophy. In the monkey, all manner of portasplenic occlusions failed to produce anything resembling the picture of Banti's syndrome, splenic anemia, or anything other than a transient portal hypertension and congestive splenomegaly. It must be said, of course, that simple ligation is quite a different process from progressive thrombotic occlusion of these vessels which is the commonly accepted manner in which the disease is produced in man.

In so far as Banti's original cases are concerned, it is probable that at least a few of the patients in whom he was interested suffered from early cirrhosis which was not far enough advanced to be detected clinically. Had it not been for the secondary splenomegaly and anemia, these patients would in all probability not have come to his attention. Others of his patients undoubtedly had portal hypertension due to portasplenic thrombosis. Thus, Banti described

portal hypertension primarily without, in effect, distinguishing between whether the block was inside or outside the liver Today it makes relatively little difference whether the term Banti's disease, or more properly Banti's syndrome, is retained or not If it is to be used at all, it had best be restricted to portal hypertension due to extrahepatic block

The Eck Fistula in Man

The application of the Eck fistula to portal decompression in man epitomizes the art and the science of modern surgery. The unfortunate delay of twenty-five or so years which generally takes place between the development of an operative technique in the experimental animal and its application to man is evident The crucial role modern supportive therapies have played in making the operation a successful routine is also manifest Cryptically stated, the first phase of portal decompression might be characterized as making the operation safe for the patient, the second as making the patient safe for the operation Eck devised his fistula in the dog in 1877. Twenty-five years later, Vidal first performed this operation successfully in man Forty years passed before Whipple and his group at the Presbyterian Hospital in New York City standardized portal decompression for man

As emphasized earlier, Eck had two objectives in devising his fistula first, to oppose those who held that the dog would die were portal blood flow through the liver to be interrupted, second, to

he had the relief of increased portal pressure specifically in mind Nor did he mention that his fistula might be useful for the treatment of esophagogastric hemorrhage

The original suggestions of Eck escaped attention until 1902, when they were taken up by Tansini who successfully repeated Eck's experiments in dogs However, instead of employing a side-to-side anastomosis and then ligating the portal vein on the liver side of the

upon the experiments of Tansini, Lenoir in 1912 undertook a portacaval shunt in man in the end-to-side position As far as can be determined, this was the first time that portal decompression was performed in this fashion Unfortunately, this patient died in anuria forty-eight hours after operation.

In rather rapid succession a number of continental surgeons

interested themselves in portacaval shunting As their reports are studied, it is difficult to determine the exact chronological order, for the cases operated upon were not reported separately but were often merely recorded *during discussions at one or another of the* clinical conferences of the day All of the men to be mentioned in the next few paragraphs did their work somewhere between 1900 and 1918 It is remarkable how reminiscent of today's problems are some of the controversies which took place over fifty years ago

Franke's insistence that the fistula must be performed between the portal vein and the vena cava became associated intimately with the results of Jerusalem's experiments in which the rationale of the use of a true Eck fistula (i e with ligature of the portal vein liverwards) was challenged Jerusalem summed up both sides of this question in the following words. "The possibility had to be considered that, in the first place, part of the portal vein blood would not be sufficiently detoxicated because of the detour around the *liver and, in the second place, that the blood from the vena cava* inferior with its rich store of adrenalin, might, on reaching the liver, cause pathological changes there Exhaustive research, though not yet completely finished, has gone far to prove that these fears were unfounded The animals, after operation, showed no deficiencies whatsoever and various methods of determining the adequacy of liver function showed no loss of function." In other words, Jerusalem, by omitting the ligature of the portal vein liverwards, devised the first "false" Eck fistula—a shunt which permitted the portal bed to

accessible for suture and Jerusalem's claims for the advantages of his "false" Eck fistula, the so-called Franke-Jerusalem operation came into recognition as the most anatomically and physiologically sound operation devised up to this time

During this period, Beer claimed that he had attempted this procedure twice but in each instance he had to abandon the effort, once because of enormous peritoneal adhesions, and once because of severe hemorrhage De Martel reported carrying out the operation on a human patient who died a few hours later from renal insufficiency

Jeri

As

anastomosis of the portal vein and the inferior vena cava has been successfully performed in a living man It may, therefore, be of interest to show you a patient in whom *I* anastomosed *(these vessels)*

for cirrhosis of the liver with ascites and who has, as you will see, survived the operation very well." Although Rosenstein carefully points out that the immediate results of the operation were poor, there were indications five months postoperatively that the procedure was not entirely unsuccessful. At this time, the rate and amount of ascitic fluid formation seemed to be decreasing appreciably. Modestly, Rosenstein pointed out that it required great skill and deftness to place the continuous sutures in the vessels.

While surgeons were working upon the problems of major shunts, a number of men concerned themselves with lesser procedures designed to decompress the portal venous bed. Bogoras successfully sutured one of the lesser mesenteric veins to the vena cava. He reported that the spleen became noticeably smaller and the ascites disappeared. Gunn attempted unsuccessfully to anastomose the portal vein to the ovarian vein, and Villard and Tavernier (1910) created an opening between a branch of the superior mesenteric vein and the ovarian vein. So narrow was this anastomotic channel that these authors finally recommended that the inferior mesenteric and ovarian or spermatic vein be used. Muersing (1912) established a communication between the portal and systemic circulations by suturing the splenic and spermatic and the coronary and suprarenal veins. By and large, these small vessel anastomoses seemed so uniformly doomed to fail that reports even of their successful performance were never very enthusiastically received.

In their search for successful small and large vessel anastomoses, it is apparent that most of the men concerned were well aware of the physiological and technical problems which plague those interested today in portal decompression. For instance, Enderlen and his associates in their extensive monograph covering the entire subject pointed out that harm will not be done in carrying off portal blood for "little enough has been passing through the vessel." These men also observed that in dogs, the venovenous connection might close without disturbing the dog. Under these circumstances, the entire portal flow would be carried through the collaterals. Rosenstein suggested that one of the reasons for unsatisfactory results in his successfully performed shunt might well have been its closure. Tansini and Lenoir caused a considerable furor by proposing an end-to-side shunt. It was argued (ineffectively however) that neither men nor animals could survive without the immediate detoxicating action of the liver upon the portal vein blood. The danger of completely occluding portal and caval flow which predominated early thinking about these various operations, led many to devise ingenious clamps of one design or another to permit blood to flow through these great vessels during the course of fashioning the shunt.

In his discussion of de Martel's announcement of an unsuccessful portacaval shunt, Vidal in 1910 expressed the opinion that ascites is due to portal phlebitis and not to increased pressure. Hemorrhages, on the other hand, Vidal maintained are caused by elevated levels of portal pressure. This casual reference is one of the earliest indications that a few men at least conceived of portal decompression as an operation primarily useful in portal hypertension and its attendant hemorrhages rather than in the treatment of ascites. Bogoras and others made the sage observation that one of the important complications of all of these operations was diminished urinary output. This they tentatively ascribed to impeded outflow of blood from the renal veins caused by the greatly increased inflow of blood into the cava from the plethoric portal system. Of especial note was Enderlen's insistence that, "The operation be not undertaken in patients in such poor condition as to make it dangerous to life; there must be the assurance that the patient can survive, or else the procedure will be discredited."

The present-day application of the Eck fistula to the treatment of portal hypertension in man was developed in the Spleen Clinic of the Presbyterian Ho [illegible] under the direction of [illegible] staff were drawn from [illegible] atology, and pathology [illegible] published his first report on the abnormal physiology of the portal venous bed. He and Caughy undertook the measurement of the pressure in the splenic vein in certain cases of hepatosplenomegaly. In some instances, this was found markedly elevated above normal. In 1942, therefore, Rousselot and Whipple again attempted the decompression of the portal bed by fashioning an anastomosis between it and the general systemic circulation. Their initial efforts to anastomose a small portal to a small systemic venous radicle failed, even as such efforts had failed in the past. Rousselot then had to enter army service, and Whipple and Blakemore continued to study the problem of portal decompression in man.

The technique initially employed by these two surgeons was similar in design to one devised many years earlier for the dog by Quierolo (1895). This early experimenter everted the cut end of the portal vein over a glass tube and introduced this vessel and its prosthesis into an opening in the vena cava where it was held in place by a purse-string suture. Instead of using a glass tube, Whipple and Blakemore employed small vitallium tubes similar to those Blakemore and Lord had devised for the end-to-end approximation of arteries. Apparently, neither Blakemore nor Whipple was aware of Quierolo's work

until they had successfully completed shunts upon six human patients

Not long after the initiation of the modern era in portacaval shunting, Blakemore and others became dissatisfied with the prosthetic technique because of a high incidence of thrombosis They turned, therefore, to the everting suture technique so successfully applied to arterio-arterial anastomosis by Blalock, by Gross, and by Humphreys In addition, curved rubber-shod clamps similar to those de-

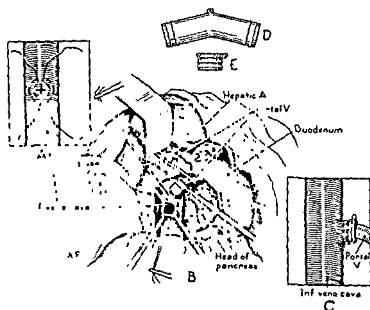


Fig 67 Blakemore's original technique for a portacaval shunt Although a vitallium prosthesis was employed for the original shunts, this technique was soon abandoned in favor of a direct suture type of anastomosis

vised by Jerusalem many years earlier were designed to permit the construction of the anastomosis without obstructing caval blood flow In their original procedures, Whipple and Blakemore employed either splenorenal or direct portacaval shunts The original illustration of their techniques is reproduced in Figure 67 In fashioning the splenorenal shunts, Blakemore advocated that the kidney be removed and that the anastomosis be performed between the ends of the splenic and renal veins. Linton showed that this was not necessary and demonstrated that an entirely satisfactory shunt could be formed between the end of the splenic and side of the renal vein without sacrificing the kidney On the basis of Whipple and Blake-

more's demonstration that portal decompression was an entirely feasible procedure, the operation in one or another of its many modifications has been widely practiced both in this country and abroad

The Hepatic Veins

In man, obstruction of the hepatic veins due to one or another cause has been recognized as a clinical syndrome for well over a hundred years Since Budd's original description in 1845 and Chiari's careful study appearing in 1899, about a hundred carefully documented case reports have appeared in the world's medical literature In general, this disease is due either to a primary endophlebitis of the hepatic venous drainage system or to obstruction of the main hepatic veins by a benign or a malignant tumor or by an abscess forming either within or without the liver In its acute form, it is characterized by the sudden appearance of abdominal pain, nausea, and vomiting The liver and spleen enlarge rapidly, massive ascites appears, and death in hepatic coma supervenes within one to four weeks In its chronic form, the course is similar though protracted over many months to years. It is well recognized that if the patient survives long enough, portal hypertension and bleeding esophago gastric varices may develop

In view of the striking picture presented by patients suffering from sudden or progressive occlusion of their hepatic veins, it is not surprising that numerous efforts have been made to reproduce the syndrome in experimental animals Because the hepatic veins are short and enter the vena cava over a relatively wide area, most investigators have been content to produce hepatic venous congestion by wholly or partially occluding the vena cava just above the liver Bolton in 1931, Simonds and Brandes in 1925, and Brandes in 1929 all experimented with sudden hepatic venous occlusion in the dog They showed that systemic arterial pressure falls precipitously, that there is marked venous engorgement of the liver, spleen, and intestinal tract, and that the rate of flow of lymph in the thoracic duct increases enormously The dog dies within a very short time even as he does after portal venous occlusion

In our laboratory, having shown that the monkey survives portal venous occlusion, we became interested in whether or not this animal might survive hepatic venous occlusion With difficulty a technique was developed whereby the hepatic veins alone could be occluded without [illegible] monkeys [illegible] hepatic venous occlusion Apparently, this animal was [illegible] to withstand the occlusion than was the dog It appears obvious that both of these animals succumb to depletion of their circulating

blood volume into the hepatic and splanchnic venous beds. Although in the monkey the preexisting collaterals are adequate to decompress the portal system alone, they appear inadequate to carry the added burden of l
of hepatic
liver itself, [illegible]
portal system The complete details of these experiments appear in Appendix 4

Of physiological importance is the extensive series of experiments in which the vena cava has been partially or progressively occluded just below the diaphragm This, of course, not only produces hepatic venous back pressure, but retards blood flow in the cava as well This latter circumstance detracts somewhat from the value of these studies, for it introduces reactions over and above pure hepatic congestion The stimulus to perform this type of experiment has been the observation that hepatic venous obstruction surpasses all other etiologic factors in the rate at which ascites is formed Originally, these excesses of ascitic fluid were explained upon a basis of venous mesenteric congestion Although additional factors in the formation of ascites (low serum albumin and sodium retention) have been demonstrated, even these did not seem adequate to explain the degree of ascites in hepatic venous obstruction This observation, together with the knowledge that hepatic lymph flow increased when the hepatic veins were occluded, led several investigators to postulate that in addition to the known factors, the hepatic lymphatics might contribute heavily to the formation of ascites not only in Budd-Chiari's syndrome but in the common forms of cirrhosis as well Largely on the basis of the studies of Volwiler, Grindlay and Bollman, and others it can be accepted as proved that the hepatic lymphatics contribute importantly to the formation of ascites in hepatic disease

Of particular interest in this connection are the recent investigations of Madden in which "a series of digestion experiments were performed in ten fresh cadaver specimens It was postulated that if the normal and the diseased livers could be injected with varying colored solutions of liquid latex and the surrounding parenchyma
rculation could be
Type 571 supplied
olored solution was
used for the injection of the intrahepatic systemic venous system, and a yellow colored solution for the intrahepatic portal system, and a red colored solution for the intrahepatic arterial circulation The parenchyma was then digested with commercial HCl (30%). Ten liver specimens were so injected and digested. In five, cirrhosis

of the liver with ascites was present. In three, cirrhosis of the liver without ascites was present In the remaining two, the livers were normal. In cirrhosis of the liver with ascites there was no deficit in the intrahepatic portal bed On the contrary there was an absolute increase in the intrahepatic portal bed However, there was a marked absolute decrease in the intrahepatic systemic venous bed, so much so that a reciprocal pattern existed between the increase in the intrahepatic portal bed and the decrease in the intrahepatic systemic venous bed On the other hand, in cirrhosis of the liver without ascites there was a symmetrical pattern between these two systems characterized by a symmetrical deficit in both the intrahepatic portal bed and the intrahepatic systemic venous bed. Accordingly these studies would confirm both Herrick and McIndoe From the studies it is postulated that Herrick must of necessity have perfused specimens of cirrhotic livers in which there was, clinically, an associated ascites This would explain logically the reason why, gram for gram of liver substance, a greater amount of perfusion fluid was used By the same reasoning one can also confirm the work of McIndoe by postulating that McIndoe must of necessity have perfused specimens of cirrhotic livers in which, clinically, ascites was not an associated finding Since our perfusion studies in cirrhosis without ascites have shown a constant finding of an intrahepatic deficit in both the portal and the systemic venous systems, it would explain both the diminution in the volume of perfusion fluids used compared to normal, and the portal bed deficits demonstrated by McIndoe in his digestion experiments The studies would also confirm the experiments of Dock who, as previously stated, confirmed the work of both Herrick and McIndoe We postulate that in the four liver specimens used by Dock, clinically, ascites was present in two and absent in two

"From this study we postulate that the pathogenesis of ascites in cirrhosis of the liver is not primarily an intrahepatic portal bed block, but it is primarily an intrahepatic systemic venous bed block An

exists but this is only

tflow tract, namely, the

The Hepatic Artery

It would be logical to assume that the portal vein, in view of its size and unique position in between two capillary beds, would have attracted the attention of experimental physiologists long before the hepatic artery, but such was not the case In 1699 a no lesser scientist than Malpighi became interested in the relationship of hepatic arterial blood flow to the secretion of bile He showed in a

series of acute experiments performed upon the dog that occlusion of the hepatic artery did not affect the flow of bile from the common duct Henle and Heidenhain repeated these experiments many years later and disagreed with Malpighi, they believed they were able to show that interruption of the continuity of the hepatic artery resulted in the abrupt cessation of bile flow As mentioned in the historical introduction, another bit of early evidence concerning the relationships of bile formation to blood flow was obtained from a patient whose portal vein emptied directly into the vena cava without passing through the liver Since this patient was known to have secreted bile non

dences to the co

secretion of bile

tion to hepatic arterial flow is not even yet considered closed is attested by the recently reported experiments of Hermann, Jourdan and Sédallian These investigators, dissatisfied with previous experimental studies, devised an ingenious cross circulation preparation in which the liver received its arterial blood flow from the artery of another dog In this preparation bile, normal in every respect, was *promptly secreted upon establishment of the new circulation* Of perhaps more than passing interest in connection with these experiments was the observation made by these investigators that is reminiscent of Macgraith's "red" and "blue" preparations referred to in the section dealing with the effects of epinephrine upon the liver Hermann, Jourdan and Sédallian noticed that if their preparations were *not* set up deftly and quickly, the livers of some of their animals never regained a normal ruddy appearance Instead, they remained dull, shrunken, and lifeless

Practically all of the early experiments upon the hepatic artery were acute, it was many years before investigators became interested in what would happen to the animal as a whole were its liver deprived of arterial blood Simon de Metz in 1828, Kollman in 1857, and Cohnheim and Litten in 1876 studied hepatic arterial occlusion in the pigeon, dog, frog, and rabbit respectively The effects were variable the pigeon was unaffected; fatty degeneration was reported in the frog; and the dog and rabbit died Betz in 1863 antedated

of the gastroduodenal artery did the dog die

What may be termed the modern era in the study of the physiology of the hepatic artery began in 1909 with the work of Haberer and Baudouin Both these men showed that most common laboratory animals die following complete interruption of their arterial blood

flow Although these animals were just as certain to die as were those with their portal veins ligated, it was evident that the time relationships differed sharply. Following portal ligation the cat and dog died within a matter of minutes or at the most hours On the other hand, death did not follow hepatic arterial ligation for a period of many hours or even several days In addition, the difference on postmortem examination between the livers was striking: little if any change was noted after portal ligation, whereas after arterial occlusion the liver was necrotic The success of these early experiments in producing hepatic necrosis was dependent upon how completely the liver was deprived of its oxygenated blood

Early Haberer emphasized that in order to produce hepatic necrosis in the dog, the duodenal and the right gastric as well as the several hepatic arterial branches must be securely ligated. From this early date on, all interested in the physiology of the arterial supply to the liver have realized that partial dearterialization of the liver is ineffective Not only can small collateral channels be overlooked,

sion In the dog, Shaw, Fraser and his associates, Davis and Tanturi and others have shown that the mortality of apparently complete intrahepatic dearterialization is about 35 per cent As a result of many experiments it has been learned that one of the most valuable criteria of complete dearterialization of the liver is necrosis of the gallbladd[illegible]
that the [illegible]
demonstr[illegible]
containe[illegible]
ligation of the hepatic artery, there appeared a few years later many

[illegible]
Boyce and McFetridge decided from their studies that death was caused by the liberation of toxic material from postmortem enzymatic degradation of the liver proteins The next contribution to this subject appeared in 1916 when Narath again demonstrated that all of his
when he [illegible]
vein, the [illegible]

Save for these relatively infrequent experiments, interest in the hepatic artery did not again become apparent for almost twenty

years As related in the Eighth Macy Conference on Liver Injury, Markowitz, after being interrupted by the war, again took up his studies on arterialization of the liver after ligature of the hepatic artery Working indefatigably on this subject, Markowitz successfully created arteriovenous fistulas between the aorta and the portal vein, between the aorta and vena cava and, combined with a reverse Eck fistula, between the splenic artery and vein, and between the hepatic artery and portal vein Because these techniques were only indifferently successful, Markowitz was inspired by Grindlay and Bollman's work on the hepatic lymphatics to use Transflex tubing coated inside with silicone to join the splenic artery and vein. Because he could not be sure his technique was really aseptic, Markowitz gave his animals penicillin In every instance, these animals survived hepatic dearterialization However, when the tubing used to join the hepatic artery to the vein was examined after the animals were sacrificed, it was invariably found occluded by a thrombus Obviously, the next step was to ligate the hepatic, gastroduodenal, and right

[illegible]

rupture of a gangrenous gallbladder In the animals that survived, the [illegible]

sho[illegible]
they be continued longer than five or six days Thereafter, penicillin was not needed for survival Hartroft, who studied the microscopic sections of the liver in these animals, was unable to identify any significant abnormalities This picture was in sharp contrast to that encountered in the livers of animals untreated with penicillin Here, branches of the portal vein were seen filled with masses of bacteria From these experiments, Markowitz concluded that the function of

toxins Further, he expressed the opinion that the *major organism* concerned, if it was not the Welch bacillus itself, was at least an important variant From his studies, he concluded that functionally penicillin replaces the hepatic artery *in so far as the liver is concerned* Marked atrophy of the gallbladder, however, follows complete hepatic dearterialization He found that in an extended series of dogs with dearterialization of the liver *and adequate penicillin* therapy, the mortality was about 35 per cent Half of the animals that died succumbed to perforation of the gallbladder and bile peritonitis The cause of death in the *remaining fatalities remains*

obscure Unprotected by penicillin, the mortality was regularly almost 100 per cent In these, the liver presented as a shrivelled, mushy, stinking, crepitant mass. Markowitz's original studies were promptly repeated in other laboratories over the country and his findings confirmed In addition, other antimicrobials were tried, and many of these were also shown to be effective in replacing the function of the dog's hepatic artery

As might have been expected, these experiments have led to a great deal of speculation concerning other aspects of hepatic arterial physiology, not only in the dog but also in man. For instance, it remains to be discovered at precisely what level of oxygen tension intrahepatic canine blood must be kept to prevent proliferation of anaerobic micro-organisms Of great importance is the question of how successfully the results of these experiments in the dog can be applied to man Mann, Bollman, and Grindlay have asked a most pertinent question "Why do dogs survive after penicillin has been discontinued?" They doubt that a sufficient number of arterial collaterals have developed in this short period of time On the other hand, Fraser and his associates believe that it is entirely a matter of rapid development of collateral arterial blood supply.

In our laboratory, after proving that in the majority of instances the Macaca mulatta monkey survives sudden portal occlusion, we turned to a study of hepatic dearterialization in this same animal. In 20 monkeys of this species, the hepatic artery was completely resected from its origin on the axis to its various points of entry into the liver All of these animals save one survived, clinically undisturbed by the procedure Five received a combination of penicillin and dihydrostreptomycin, while 15 did not receive antimicrobial therapy. Routine cultures of slices of their livers were performed both aerobically and anaerobically These were all negative. It has been concluded, of course, from these experiments that hepatic arterial resection in the monkey is a fundamentally different problem from that encountered in the dog The complete protocols of these

three groups of patients: those in whom the hepatic artery has been ligated accidentally, those in whom the hepatic artery has been occluded slowly by an aneurysm or tumor; those in whom the hepatic artery has been deliberately occluded as a treatment for portal hyper-

have been the site of a greater or lesser degree of infection. In the last group the liver, of course, has routinely been the site of cirrhosis

The subject of accidental ligation of the hepatic artery has been masterfully reviewed by Ritter in 1922 and by Graham and Cannell in 1933. After analyzing 27 cases previously reported and studying the 15 recorded deaths, the latter authors concluded that accidental ligation of the hepatic artery in man is always a serious, but not necessarily a fatal, catastrophe. They point out that the prospect

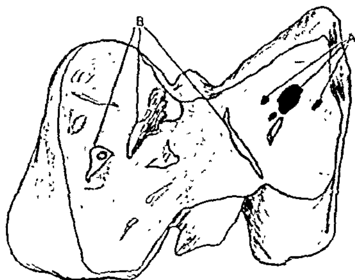


Fig 65 Graham
degree of hepatic nec
of the common hepa...
20, 1932–33)

of liver necrosis increases steadily as the point of ligature is moved toward the periphery of the arterial circuits comprising the oxygenated blood supply to the liver In sharp contrast to the dog, hepatic arterial insufficiency in man makes its appearance comparatively late after the accident This, Graham and Cannell point out, makes reexploration of the abdomen urgently *indicated* should such an accident be suspected

Of particular interest in relationship to the experiments upon the Macaca mulatta monkey is the case constituting the basis for Graham and Cannell's report This patient's hepatic artery was removed one inch from its origin on the celiac axis in the course of a gas-

obscure Unprotected by penicillin, the mortality was regularly almost 100 per cent In these, the liver presented as a shrivelled, mushy, stinking, crepitant mass. Markowitz's original studies were promptly repeated in other laboratories over the country and his findings confirmed In addition, other antimicrobials were tried, and many of these were also shown to be effective in replacing the function of the dog's hepatic artery

As might have been expected, these experiments have led to a great deal of speculation concerning other aspects of hepatic arterial physiology, not only in the dog but also in man. For instance, it remains to be discovered at precisely what level of oxygen tension intrahepatic canine blood must be kept to prevent proliferation of anaerobic micro-organisms Of great importance is the question of how successfully the results of these experiments in the dog can be applied to man Mann, Bollman, and Grindlay have asked a most pertinent question. "Why do dogs survive after penicillin has been discontinued?" They doubt that a sufficient number of arterial collaterals have developed in this short period of time On the other hand, Fraser and his associates believe that it is entirely a matter of *rapid development of collateral arterial blood supply.*

In our laboratory, after proving that in the majority of instances the Macaca mulatta monkey survives sudden portal occlusion, we turned to a study of hepatic dearterialization in this same animal In 20 monkeys of this species, the hepatic artery was completely resected from its origin on the axis to its various points of entry into the liver All of these animals save one survived, clinically undisturbed by the procedure Five received a combination of penicillin and dihydrostreptomycin, while 15 did not receive antimicrobial therapy. Routine cultures of slices of their livers were performed both aerobically a
been concluded, o
terial resection in
from that encount[illegible]
experiments are recorded in Appendix 3

ligated accidentally: those in whom the hepatic artery has been oc-
ch
ar
tension. In the first two categories, [illegible]

tion for aneurysm as compared to the less disastrous results after accidental ligation However, resolution of this apparent conflict is not too difficult if the exact location of the aneurysm is taken into account and if it is recalled that the more peripheral the lesion the greater the likelihood that hepatic necrosis will follow any attempt at its removal or ligature of its feeding vessel It is more than probable, however, that a lesion of the common hepatic artery could be

The possibility that an anomalous artery also might be present must be considered, for if it existed resection of an aneurysm might well be embarked upon with great promise of a successful outcome A vigorous approach to the treatment of these lesions is important, for they are quite as apt to rupture as are so called berry aneurysms occurring elsewhere in the body With improvement in vascular surgery, it can be hoped that in the future a resected hepatic artery may be replaced by a graft Arterialization of the portal vein, successfully practiced in the experimental animal, might also provide safety to a patient whose hepatic artery had to be resected for aneurysm or invasion by a malignant tumor Those who would hesitate to fashion a fistula between the hepatic artery and portal vein for fear of deleterious cardiac effects must remember that under these circumstances the general venous circulation is protected from the untoward effects of such a fistula by two capillary beds

At the moment, the final word has obviously not been written upon the physiology of the hepatic artery As investigations proceed, however, it can be hoped that accidents to and diseases of this important vessel may be brought successfully under surgical control

In embarking upon a discussion of hepatic arterial ligation as a form of treatment for esophagogastric hemorrhage secondary to portal hypertension, a highly controversial field is entered As a therapeutic measure this was first proposed by Rienhoff and shortly taken up enthusiastically by Berman and others Apparently, its rationale is based upon the original observations of Herrick who believed he was able to demonstrate that in cirrhosis of the liver abnormal communications developed between the hepatic arterioles and the smaller radicles of the portal venous system In this fashion, a portion of the hepatic arterial head of pressure was transferred

contributions have not been confirmed, although here and there evidence has appeared indicating that there might be some virtue in

trectomy for a pyloric carcinoma The patient died upon his seventh postoperative day, presumably from a diffuse bronchopneumonia. At postmortem examination, insignificant areas of hepatic necrosis were found in the left lobe of the liver (Fig 68). Neither was there clinical nor postmortem evidence that the ligation of the hepatic artery had in any way caused this patient's death, either directly or indirectly So closely does the picture manifested by this patient resemble that encountered in our experiments upon the monkey that there can be little doubt that man's hepatic arterial physiology resembles that of this primate far more closely than it does the dog's

Superficially it might be argued that the administration of large amounts of penicillin to man is unnecessary, save for the fact that under the circumstances in which accidental ligation of the hepatic artery is apt to overtake the unwary surgeon, hepatic infection of one sort or another is almost sure to be present Few patients with either acute or chronic biliary tract disease are entirely free of both

dearterialization due to one cause or another, that the livers of 5 contained gas This was proved to have been due to the Welch bacillus It can only be concluded, therefore, that though the human

tions the liver might be flooded with highly pathogenic organisms, prophylactic antimicrobial therapy must be considered essential whenever it is likely that hepatic arterial blood flow might have been compromised

In man, attention was probably first called to the hepatic artery by recognition of the fact that this vessel can be the site of aneurysm formation One of these interesting lesions was first described in 1856 by Ledieu in which the blood in the aneurysm had clotted and completely occluded hepatic arterial flow This latter case for the first time demonstrated that if occlusion of the hepatic artery occurs slowly enough, collaterals can completely take over the function of this vessel In a recent review of this subject Grant, Fitts and Ravdin discovered 87 aneurysms of the hepatic artery reported in the world's medical literature Of these, only 3 have been cured and they by ligation of the artery These authors found that ligation had been tried in a number of additional instances, but the mortality from liver necrosis had been so high that ligature as a form of therapy had been studiously avoided by most surgeons Superficially, it might appear difficult to explain the poor results obtained in liga-

As far as can be determined, man reacts to hepatic dearterialization *in a manner differing sharply from that in both the dog and the* monkey Complete interruption of the hepatic arterial supply to this organ in man results in massive infarction and death, generally, however, *without any evidence of intrahepatic bacterial proliferation* Only by preserving some measure of hepatic arterial flow can man survive Thus, ligation of the hepatic artery on the liver side of the gastroduodenal vessels is fatal Ligation of the common hepatic artery, however, is compatible with life There is some evidence that in patients with cirrhosis these physiological facts may be violated without endangering life

Neither the dog nor the monkey survives occlusion of both the hepatic artery and the portal vein Although such a catastrophe has never been reported in man, it seems justifiable to conclude that were it to happen, man, too, would promptly succumb to massive hepatic infarction * For practical purposes, combined hepatic arterial and portal venous occlusion may be considered fatal With the demonstration by Markowitz and others that the dog tolerates hepatic dearterialization provided the animal is protected by penicillin, Rappaport visualized a new avenue of approach to experimental hepatic ischemia He was stimulated to see whether the clinical syndrome of hepatic coma could be induced in dogs by

[illegible]

therefore devised a three-stage and later a two-stage procedure as

[illegible]

but there remained sufficient viable hepatic tissue to maintain life Clinically, these animals presented practically all of the features of non lethal hepatic decompensation In some, widespread edema appeared which could, astonishingly enough, be controlled by the liberal administration of 50 per cent glucose solution Five dogs

* Since the original preparation of this manuscript, it has been the author's misfortune to have resected the portal vein and inadvertently to have placed a ligature tightly about an aberrant branch of the right hepatic artery during an *en bloc* resection of the head of the pancreas for an advanced carcinoma At autopsy the left hepatic territory was normal, but the right was the site of a massive ischemic infarct The patient expired five days after operation with a high fever and in anuria NECH E T H #82–690

reducing hepatic arterial inflow Dock, as a result of his studies, concluded that, "In treated alcoholic cirrhosis, with ascites or danger of fatal hemorrhage, procedures to reduce hepatic inflow may be worth consideration " Opposing these two views, of course, are those of McIndoe who believed that liver failure ultimately occurred when hepatic blood flow, first portal and then hepatic arterial, all but ceased. If this be true, hepatic arterial ligation could hardly be recommended

As the reported cases of hepatic arterial ligation are reviewed, great disappointment as to the immediate effects on life is apparent That some patients survive undisturbed is obvious, that others die within a few days of diffuse hepatic necrosis is equally apparent. In the fall of 1952 at the Surgical Forum meetings of the American College of Surgeons, current opinion was well summed up in the discussion of several papers on this subject. It was the consensus that hepatic arterial ligation might ultimately be proved feasible and beneficial in certain patients with cirrhosis Up to the present time, techniques for the proper selection of cases have not been developed In spite of the many controversial aspects of this problem, it seems reasonable to conclude at the moment that the patient with cirrhosis probably tolerates hepatic arterial occlusion better than does normal man The therapeutic application of ligation of the hepatic artery will be discussed further under the treatment of portal hypertension

SUMMARY OF EFFECTS OF HEPATIC ARTERIAL AND/OR PORTAL VENOUS EXCLUSION

In the preceding sections, the effects of complete exclusion from the liver of either portal or hepatic arterial inflow were reviewed As far as can be determined by the methods available today, the liver tolerates total exclusion of portal flow very well. Only one of its normal faculties is lost—the power to regenerate By portacaval transposition, however,
turned almost, if not ent
hepatic regeneration ma
of blood flowing through the liver than to any specific factor contained only in portal blood

Hepatic dearterialization by resection of the hepatic artery is fatal to dogs unless intrahepatic proliferation of the Welch bacillus (an organism indigenous to this animal's liver) is prevented by one or another of the antimicrobials to which this organism is sensitive. In sharp contrast to the dog is the Macaca mulatta monkey, for its liver does not normally harbor pathogenic organisms. Here, resection of the hepatic arterial tree together with all its twigs is not fatal.

amount of blood delivered by the hepatic artery, produced an experimental preparation in which torrents of arterial blood were passed through the liver without at the same time increasing portal pressure. This was accomplished by means of a vein graft connecting the side of the aorta with the hepatic end of the portal vein. The

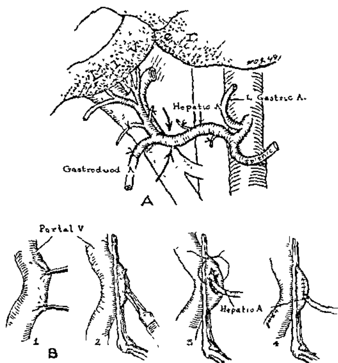


Fig 69 Implantation of hepatic artery into the portal vein (dog). In A is demonstrated by two arrows the point selected for implantation. In B is outlined the technique of implantation. (From Schilling, McKee, and Wilt Surg., Gynec & Obst., vol 90, 1950.)

splanchnic end of the portal vein was implanted into the vena cava as an end to side Eck fistula. An aortogram obtained by Cohn and Herrod six weeks after establishing such a double shunt is reproduced in Figure 70.

Several important comments may be made upon this type of arteriovenous fistula. It is entirely possible that should it become necessary to resect the hepatic artery for an aneurysm or should the vessel be irreparably damaged during an upper abdominal operation, hepatic necrosis could be prevented by arterialization of the portal

subjected to this technique died after thirty-one to ninety-six hours in coma. Five additional animals were in coma from three to seven days and then recovered The success of the experiments depended upon the care with which the stages were spaced. As a result of these investigative efforts, Rappaport expressed the conviction that the clinical picture appearing in these animals had many features in common with that of human patients suffering from comparable degrees of hepatic ischemia Worthy of comment is the fact that many years ago McIndoe predicated hepatic failure on final failure of its blood supply. By adding carefully controlled biochemical studies on the blood and plasma in these animals, Rappaport expressed the hope that the biochemical pathology of hepatic failure and coma may be clarified

ARTERIOVENOUS FISTULIZATION OF THE PORTAL VEIN

As long ago as 1916, Narath, well aware of the fatal consequences of hepatic dearterialization in both man and dog, designed a number of experiments to discover whether the liver of the dog could be arterialized by way of the portal vein He attempted to implant either the hepatic artery or renal artery into the portal vein in a large series of experiments Only two animals survived any appreciable length of time, thrombosis developing in the fistulas of the majority of his animals The experiments, however, convinced this early investigator that the liver could indeed survive were sufficient arterial blood carried to it by way of the portal vein

Little further interest was expressed in this type of experiment until over fifteen years later when Naegeli attempted to arterialize the portal system by means of a fistula between the hepatic artery and superior mesenteric vein The majority of his experiments were unsuccessful as were those of Ghiron and Badalla who used the splenic vein and hepatic artery. Markowitz's recent interest in arterializing the portal vein led directly to the discovery that the hepatic artery could be ligated successfully in the dog provided this animal was given large doses of penicillin Schilling and his associates believed that if a proper technique could be devised, the portal vein could be arterialized This they accomplished in 1950 by implanting the hepatic artery into the side of the portal vein. Their original illustrations demonstrating their method are reproduced in Figure 69A and B Many of Schilling's animals survived up to eighteen months At the end of this period, there was no evidence of mesenteric congestion, increased portal pressure, or cardiovascular abnormalities. Liver function was normal.

The most recently developed method for arterializing the liver is that of Cohn and Herrod. These men, dissatisfied with the small

CHAPTER 13

Portal Hypertension

HISTORICAL

ANY essay proposing to consider the early history of portal hypertension must of necessity deal with a number of exasperating vagaries Probably the most difficult of these to interpret correctly is whether or not the physicians of years ago appreciated that splanchnic congestion, hemorrhoids, esophageal varices, and even ascites were a more or less direct consequence of elevated portal pressure Certainly it is true that these terms were then in everyday usage But equally certain is it that neither portal hypertension nor elevated portal pressure was ever clearly defined at a very early date If it be accepted that one or a combination of these descriptive terms may *be interpreted to mean that patients manifesting these various clin*ical signs were known to have a high portal pressure, then the origin of portal hypertension can be traced back to the early eighteenth century On the other hand, if the only acceptable criteria of knowledge of elevations in portal pressure be the use of the term portal hypertension, then the first awareness of the existence of this phenomenon appeared during the first quarter of this century, almost three hundred years later

For instance, as early as 1748, Stahl apparently observed that somehow the portal vein, the spleen, and hemorrhoids were related in a vague disease syndrome In studying Stahl's half medical, half metaphysical descriptions of disease, it is difficult indeed to decide just what this great German thought about the various clinical conditions known today to be manifestations of elevations in portal pressure Furthermore, in reviewing the medical dissertations of other great German physicians such as Koeniff and Raikem, it seems [illegible] circulation, and splanchnic venous dilatation It seems to have been

vein Were such a fistula to be created, the question might well be asked whether the undesirable cardiac sequelae of a systemic arteriovenous fistula should be anticipated Probably not, for a capillary bed would be interposed between the fistula and the low pressure



Fig 70 Arteriogram demonstrating complete arterialization of the liver by means of an end-to side autogenous venous graft situated to the liver end of the portal vein and the side of the aorta By this technique Cohn and Herrod demonstrated marked engorgement of the liver, under which circumstances, however, the liver was able to carry on its functions normally. (From Cohn and Herrod Surgery, vol 32, 1952)

systemic venous system. Whether this would protect man from cardiac failure is not known. Cohn and Herrod's intimation that cirrhosis of the liver might be benefited by increasing the arterial blood supply by means of such a fistula is an intriguing suggestion which as far as is known has not yet been tried.

to portal venous obstruction Enderlen wrote that, "If hepatic cirrhosis antedates the thrombosis and as a consequence of the compromised intrahepatic circulation the esophageal veins are dilated, then over-filling of these veins must lead to rupture and immediate esophageal hemorrhage If cirrhosis is not present, hemorrhages occur much later and are less dramatic" At this same time, it was recognized that when mediastinal and cervical collaterals were unable to transfer the blood of the overburdened portal system to the mediastinum, the "congestion passes into the nasal vein and nosebleedings ensue" (Enderlen)

Preble, in 1900, presented a well documented report of 60 patients with cirrhosis of the liver who succumbed to massive gastrointestinal hemorrhage In 80 per cent of these patients, varices were demonstrated at the time of autopsy, and in many the actual site of erosion from which the hemorrhage occurred could be demonstrated Even Preble, however, was unsure as to precisely what was the cause of bleeding He, therefore, expressed the opinion that in patients with varices which had developed in response to portal obstruction, the hemorrhages possibly represented an expression of an acquired hemorrhagic diathesis As Preble's writings are reviewed as a whole however, it is evident that he believed that the varices appeared in response to increasing increments of pressure within the portal system In an effort to explain what he assumed to be an obvious interference with portal blood flow, he hypothetically implicated the loss of elasticity of the liver, which was well recognized as a feature of cirrhosis

About 1912 interest in portal pressure abated, and little important reference to the subject can be found until many years later In 1928 McIndoe, whose painstaking experiments on cirrhosis have been referred to elsewhere, reached the conclusion that the portal pressure must be elevated and he also used the term portal hypertension Furthermore, he encouraged the surgical world to pay greater attention to this disease and to try to reduce the pressure by forming a fistula between the portal vein and the vena cava A few years later McMichael became interested in congestive splenomegaly and, reasoning from pulmonary hypertension, decided that the changes seen in the veins of the splanchnic bed and spleen could most logically be explained upon a basis of elevated portal pressure The term portal hypertension also found favor in McMichael's eyes

With these many indirect evidences as a background, Rousselot in 1936, and Thompson, Caughy, Whipple and Rousselot in 1937, reported that they had actually succeeded in measuring the pressure in the splenic vein of patients with enlarged spleens who also pre-

unthought of that cirrhosis caused obstruction to portal blood flow unless portal thrombosis appeared to complicate the primary disease As far as extrahepatic block was concerned, this seems to have been overlooked entirely during these early days

In so far as varices of the esophagus are concerned, it is obvious that their clinical importance was barely recognized until somewhere about the middle of the nineteenth century In this country, Power was one of the first to describe accurately massive hemorrhage from esophagogastric varices In 1840 he reported the autopsy findings upon a colored man who died after a long series of esophageal hemorrhages Power described a large plexus of tortuous and dilated veins at the lower end of this man's esophagus. In one of these, he noted a large ulceration from which he could express copious amounts of blood He wrote, "Varicose veins of the esophagus I have never met with before, nor have I found any similar case recorded, they may sometimes exist to a lesser degree, but I doubt whether their presence to such an extent, and death caused by their rupture, be not something as yet unheard of in pathological anatomy" Although Power concluded his report with a detailed description of the stomach, heart, and other organs, he failed to mention the liver or the spleen, nor did he intimate that hemorrhage was in any way associated with increased portal venous pressure. Upon this report, Power based his claim that in publishing it he had recorded for the first time a patient who had died of hemorrhage from varices of the esophagus

On the continent, Fauvel in 1858 described a case similar to Power's So rare was this considered that when Frerichs a few years later published his extensive monograph upon the liver, he referred to Fauvel's case as the only one upon record of bleeding from esophageal varices that he, Frerichs, had ever heard of. Despite his masterful discussion of diseases of the liver, it is impossible to be entirely sure that Frerichs associated varices and hemorrhage with liver disease or with the portal vein

Around the turn of the century, it became obvious from the writings of a few men that the concept of elevation in portal pressure was becoming more concrete In about 1900, Gilbert and Weil, Villaret, and Pichancourt (1913) interested themselves in the pressure of the ascitic fluid in patients with ascites They found that this often measured as high as 300 to 400 mm of saline From this, they reasoned that the pressure in the portal venous system must be elevated In making this assertion, these men were actually the first to use the term portal hypertension Heller, Josselin de Jong, and Enderlen all indicated that varices of the esophagus form in response

japonicum often leads to cirrhosis of the liver, and in a large majority of these patients exsanguinating hemorrhages from esophageal varices are seen. Lazzari and Rack, Minot, and Dunlap and his associates have reported severe degrees of portal hypertension occurring in patients with hepar lobatum, Boeck's sarcoid, and hemochromatosis. As time goes on, other causes of portal hypertension will undoubtedly be disclosed. It must be mentioned that there are those (Reich) who believe that portal hypertension originates as a diffuse, widespread sclerosis of the entire splanchnic venous bed, both intrahepatic and extrahepatic.

In turning to Whipple's second classification, that of extrahepatic portal block, an interesting array of pathological entities is encountered which may lead either to septic or bland thrombosis of the portal, superior mesenteric, or splenic veins. Trauma was early recognized as a definite factor. Heller in 1904 reported that a young carpenter thirty-six years of age, after jumping three-quarters of a meter into a boat, suddenly felt faint and lapsed into unconsciousness. Shortly thereafter, he vomited a small amount of bright red blood. Two years later, he succumbed to a massive gastric hemorrhage, and at autopsy an extensive thrombotic process in the portal vein was discovered. Although varicose veins were not specifically described, the patient's gastrointestinal tract was filled with blood, and the spleen was tremendously enlarged. One of Whipple's earliest cases was that of a young policeman who was struck in the epigastrium by the shaft of a runaway wagon. This patient early developed the typical picture of a traumatic cyst of the pancreas. Later he presented the classic signs of congestive splenomegaly.

Mesenteric thrombosis involving the portal vein is known to occur following operative procedures within the pelvis. It is well recognized that thrombosis of the splenic vein is one of the important complications following splenectomy. Mesenteric pylephlebitis is one of the major causes of portal venous thrombosis and was first comprehensively reviewed by W. Langdon Brown in 1901. Acute appendicitis, omphalitis, biliary infections, puerperal sepsis, and a host of other abdominal infections have been reported as the source of infected thrombi leading directly to portal thrombophlebitis. Systemic infections have also been incriminated. Mallory reported a patient whose thrombosis was ascribed to mastoiditis. Warthin ascribed the thrombi in one patient to primary anemia, while Smith and Farber attributed its development in one patient to scarlet fever. Banti felt called upon to explain the development of phlebosclerosis so often seen in congestive splenomegaly. This he did by postulating that a toxin was elaborated within the spleen which, when liberated

sented the syndrome of Banti's disease They demonstrated that here the pressure in the splenic vein was indeed elevated many times above normal With this original demonstration as a stimulus, the measurement of portal pressure became a routine observation in patients whose spleens were enlarged, whose livers were cirrhotic, and who presented either ascites or varices or both Even though this was a diagnostic test which required celiotomy, there shortly began to appear a sufficient number of portal and splenic pressure measurements to establish portal hypertension as a verifiable clinical entity.

ETIOLOGY

With the demonstration of portal hypertension as a clinical syndrome capable of producing a variety of effects such as splenomegaly and esophagogastric varices, Whipple in 1945 proposed that all patients with portal hypertension be divided into two clinical groups: those in whom the block is due to intrahepatic disease and those in whom the block lies outside of the liver. In far the greatest number of patients falling into the first category, the block is due to cirrhosis Although many theories have been proposed in explanation of the nature of the block in cirrhosis, it seems unlikely that the last word has yet been written Originally, it was thought that hepatic fibrosis so compressed the portal venules that blood flow in the presinusoidal vessels was compromised McIndoe, Madden, and others have shown that instead of the presinusoidal or portal venules necessarily being involved, just as often it is the hepatic venules which are so distorted and shrunken that they are unable to carry off from the liver normal amounts of portal venous and hepatic arterial blood. Certainly in the Chiari-Budd syndrome, which too is known to be associated with a high degree of portal hypertension, it is the postsinusoidal rather than the presinusoidal bed which is compromised. Yet another point of view has been expressed by Kelty, Baggenstoss and Butt who have demonstrated by means of wax reconstructions of the liver in cirrhosis that the lumina of many of the intrahepatic veins are partially obstructed by regenerating nodules of liver tissue Whatever the final judgment may be, it should also be recalled that clinically significant levels of portal hypertension are not necessarily an accompaniment of cirrhosis That it develops in some is obvious and has been demonstrated too many times to require further comment here It is Patek's opinion that clinically important elevations in portal pressure develop in only about one-third of patients with Laennec's cirrhosis In Ahrens's study of patients with biliary cirrhosis, portal hypertension was encountered in one-half of the patients Infestation of the liver with Schistosoma mansoni and

either within or without the liver The elevation in portal pressure is known to be the manifestation of a variety of disease processes rather than a disease in and of itself The primary clinical manifestations of portal hypertension are hemorrhage from esophagogastric varices and splenomegaly Both develop in direct response to the increased portal pressure Ascites, so commonly seen in patients with cirrhosis, does not bear as direct a relationship to elevated portal pressure as was formerly supposed Based upon good evidence, it is believed today that ascites develops as a manifestation of hepatic decompensation

Hemorrhage from esophagogastric varices due to cirrhosis may appear as a single episode and constitute the first intimation to the patient and to his physician that serious hepatic disease exists Conversely, patients who have been under treatment for cirrhosis for months or years may suddenly and quite without warning vomit a large amount of blood On occasion, the bleeding may be less dramatic and suspected only upon the appearance of a severe anemia associated with stools positive for blood In view of the fact that today most clinicians are aware that varices and hemorrhage may develop at any time during the course of cirrhosis, roentgen visualization of the lower esophagus and upper stomach is frequently performed regularly in an effort to determine whether or not portal hypertension is also developing Some concept of the incidence of bleeding in cirrhosis may be derived from Douglass and Snell's study of 444 patients with Laennec's cirrhosis reported in 1950 Esophagogastric hemorrhage, either as hematemesis or melena, occurred in 32 per cent at some time in the course of their illness In 10 per cent, massive esophagogastric hemorrhage was the initial symptom

In patients whose portal bed block is outside of the liver, a similar train of circumstances leads to the discovery of the portal hypertension A sudden esophagogastric hemorrhage may again be the first sign that the pressure in the portal vein is significantly elevated On the other hand, some suspicion of portal bed block may be aroused by the patient whose only clinical feature is an enlarged spleen In addition to bleeding and splenomegaly, attention is not infrequently called to the extrahepatic portal system by one or another of the manifestations of hypersplenism Such a patient may seek medical attention for anemia, for easy fatigability, for ready bruising, or for any one of a host of related complaints Just as a group of vague complaints may lead to a diagnosis of cirrhosis and the presence of portal hypertension may be proved or disproved by x-ray examination of the esophagus, so may an equally intangible set of clinical circumstances lead to the discovery of portal hypertension due to

caused progressive injury to the veins of the portal system. By many this sclerosis seen in the portal system was believed to be primary, but the discovery of portal hypertension has led others to the belief that these vascular changes are largely secondary manifestations. Patients with polycythemia notoriously develop thrombosis of the portal vein as part of the increase in blood viscosity and generally slow rate of blood flow which is often encountered in this disease. This tendency to thrombosis is perhaps the single factor which makes the patient with polycythemia a poor risk for a surgical procedure, and the risk is doubled in instances where a therapeutic venovenous shunt may be required

So-called cavernomatous transformation of the portal vein has long been one of the most discussed causes for portal hypertension. Although Pick was convinced that this lesion was a true hemangioma, his ideas have received little general support. Most pathologists today believe that the mass of tortuous vessels seen after portal vein thrombosis is the manifestation of recanalization and reorganization by which nature has endeavored to by-pass the site of portal obstruction Benign tumors, cysts, and congenital strictures have all been described as etiologic factors in portal obstruction. Occasionally these have led to the development of esophageal varices and severe hemorrhage Malignant tumors either primary in the biliary tract, pancreas, or duodenum, or metastases from tumors originating in the stomach, pelvis, breast or elsewhere, have all been implicated in portal venous obstruction Significant degrees of portal hypertension in relation to malignant tumors are rare, however, for generally such patients do not live long enough for varices and hemorrhage to become important clinically Perhaps one of the most interesting and as yet unsolved problems in relationship to extrahepatic block is that it has not been possible to reproduce this syndrome in experimental animals by occlusion of the portal vein by ligature. The most appropriate hypothetical explanation at the moment appears to be that in portal hypertension in man the portal occlusion develops in response to portal thrombosis which is capable of occluding not only the main venous channels, but in addition the orifices of many potential collaterals In the monkey, acute occlusion, and in the dog, chronic occlusion, is generally effected by ligature. This produces a benign type of occlusion generally unassociated with any inflammatory or extending thrombotic process

DIAGNOSIS

Portal hypertension is today believed to develop in response to obstructions to portal blood flow The point of obstruction may be

particularly if blood can be aspirated from the gastric tube, a source of hemorrhage other than varices must be suspected If such a tube is either unavailable or information derived from its use is unsatisfactory, emergency x-rays of the esophagus may be obtained without undue risk provided adequate blood replacement therapy is continued In Figure 71 is reproduced an esophagogram, obtained as an



Fig 71 E L , N E C H #75-431 Emergency esophagogram obtained in a patient who was bleeding copiously from the esophagus

emergent study in a patient with extensive esophagogastric varices from which she was bleeding massively

cannot be positively identified, for Snell has found that in 10 per cent of patients with cirrhosis either gastric or duodenal ulceration also exists Some additional help may be obtained from a Bromsulphalein test performed as an emergency Zamcheck, for instance, found that only occasionally was the retention abnormal in patients with bleeding peptic ulcer, while a normal retention was found in none of his patients in whom the hemorrhage was due to varices forming upon a basis of cirrhosis of the liver A reasonable estimate

the extrahepatic blockage of portal blood flow. To establish the incidence of esophageal varices and hemorrhage in patients with extrahepatic block is a more difficult problem than it is in cirrhosis. More than likely, many individuals live out their normal lives with occlusion of the portal vein Only those with inadequate communications between their portal and systemic circulation ever develop splenomegaly or varices Since benign splenomegaly often goes undetected, most patients with extrahepatic portal bed block first come under medical care because of an unheralded esophagogastric hemorrhage. To determine the number of patients with extrahepatic block who will develop hemorrhage is quite impossible, for there is no way of knowing how many have sustained, at one time or another, occlusion of their portal vein In cirrhosis, it has been shown that about 30 per cent of the patients develop portal hypertension It may be supposed that this complication does not appear in the remaining patients because natural portacaval communications are adequate Then it is logical to suppose that only about 30 per cent of patients with an extrahepatic block will develop esophageal varices and hemorrhage. These generalizations have by no means been proved Why certain patients with cirrhosis develop portal hypertension while others apparently do not is still a matter for conjecture and will probably continue to be so until the etiology of cirrhosis itself is clarified.

It has been made abundantly clear that hemorrhage is the most important single clinical feature of portal hypertension, yet there are, of course, many other causes of massive gastrointestinal hemorrhage When this occurs in a middle-aged patient long under treatment for cirrhosis, few problems in diagnosis appear. The clinical history, physical examination, and laboratory studies certainly point to esophageal varices as the most probable source of bleeding. Furthermore, any child or young adult who, without any prior clinical symptoms, suddenly experiences a massive hematemesis must be suspected of having bled from varices due to an extrahepatic block

A patient, however, who in the fourth, fifth, or sixth decade of life presents himself with an unheralded and severe esophagogastric hemorrhage may offer numerous complexities in differential diagnosis If the bleeding stops and an opportunity is offered for leisurely study and laboratory investigation, there is generally little reason why the source of hemorrhage cannot be detected. If, on the other hand, the bleeding continues and important clinical leads as to its source are unavailable, two courses of action are open A Sengstaken-Blakemore tube may be inserted and inflated to the proper pressure If this controls the bleeding and blood cannot be aspirated from the stomach, a presumptive diagnosis of hemorrhage from esophageal varices is certainly justified. If the bleeding continues and more

blood vessels. A number of observations support these beliefs Points of erosion have been demonstrated many times to be the actual site of hemorrhage In addition, although enormous varices of the coronary and other collaterals have been demonstrated upon innumerable occasions, reports of hemorrhage from one of these vessels are extraordinarily rare In fact one of the few authenticated cases of rupture of intra-abdominal veins is that of Feldman and Gross, who in 1935 reported a patient with portal obstruction who died of a fatal hemoperitoneum due to rupture of a retroperitoneal varix

For many years, it has been recognized that obstruction to portal blood flow gives rise to numerous more or less extensive collateral venous channels In patients in whom these can be detected clinically, a valuable aid in establishing the presence of portal hypertension is provided In both intrahepatic and extrahepatic block, collaterals characteristically develop in the following locations

1 At the two ends of the gastrointestinal tract where glandular epithelium unites with squamous epithelium, namely, at the gastric cardia and the anus Esophagogastric varices form in the submucosa at the site of anastomosis between the coronary system and the azygos, hemiazygos, and diaphragmatic system of veins Conventionally, the varices have been thought to be limited to the esophagus, but recent experience gained in demonstrating these dilated vessels roentgenographically has emphasized that they may occur as frequently in the cardia of the stomach The anastomosis between the superior hemorrhoidal vein of the portal circulation and the middle and inferior hemorrhoidal vein of the caval circulation form hemorrhoids which only occasionally become significant in the management of the patient with portal hypertension

2 At the umbilicus Here the partially obliterated embryological circulation in the falciform ligament connects the portal bed with the veins of the anterior abdominal wall As this collateral circulation develops, huge venous channels conduct blood to the systemic circulation through the branches of the lateral thoracic and epigastric veins.

3 At the sites within the abdomen where, during development, the gastrointestinal tract and its appendages become retroperitoneal (veins of Retzius)

4 Occasionally an extensive collateral circulation may develop where abdominal viscera have become adherent to the parietal peritoneum as a result of an inflammatory process

When the obstruction to portal flow lies outside the liver, numerous anastomotic channels develop in the immediate vicinity of the occluded portal or splenic veins These partially circumvent the block, and portal blood gains access to the liver almost directly. The

of the number of patients who bleed from esophageal varices as opposed to all other causes may be obtained from White's report of 400 patients with massive gastrointestinal tract bleeding admitted to the Boston City Hospital White demonstrated varices in 64 In every such series a number of patients will always be found in whom the source of hemorrhage is never discovered. This was true of 24 per cent of Snell's patients and in 5 per cent of White's large series

So important has roentgen examination of the esophagus become that it may be stated almost categorically that unless esophageal varices can be demonstrated by x-ray, clinically significant degrees of portal hypertension do not exist Whether this is entirely true is open to question The degree of success with which varices are demonstrated frequently depends upon the skill of the roentgenologist. Furthermore, it has been repeatedly shown that a diagnosis of varices can safely and easily be made by esophagoscopy. The technique by which the varices are demonstrated is probably of no particular significance, roentgenographic techniques are simpler for the patient though they may be somewhat less accurate than direct visualization. The important fact is that their presence means, in the majority of instances, that the patient is suffering from portal hypertension, a state which is a threat to his life

For many years, the opinion has been commonly held that hemorrhage from esophageal varices was precipitated by a number of ill-defined factors Sudden elevation in portal pressure due to straining was commonly advanced in explanation of the sudden hematemesis characterizing this syndrome Sharp particles of food, alcohol, and a host of apparently untoward circumstances have been incriminated Upon critical examination, all of these explanations are found wanting, and it has been well substantiated that the most important precipitating cause of hemorrhage is acid peptic erosion Presumably the varices interfere sufficiently with the function of the esophagogastric sphincter to facilitate regurgitation of gastric juice into the lower esophagus The peptic esophagitis so produced leads to small areas of actual ulceration This syndrome, of course, occurs not infrequently in association with other abnormalities in or about the diaphragm and leads to modest degrees of esophageal hemorrhage

The nature of the serious hemorrhages resulting from esophageal varices in the patient with portal hypertension undoubtedly depends simply upon the large volume of blood existing just beneath the mucosa and upon the abnormally high pressure in these large thin-walled vessels The opportunity for severe hemorrhage must be many times greater than even remotely possible from normal esophageal

portal hypertension is the demonstration roentgenographically or by esophagoscopy of esophagogastric varices Although varices have been reported in this area in the absence of portal hypertension (in children by Smith and Farber, and Jorup, and in adults by Rack, Mincks and Simeone), the instances seem to be rare indeed In

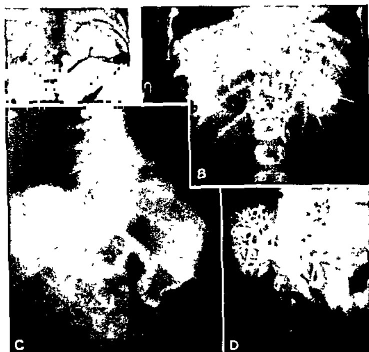


Fig 72 A One of Leger's original films Here the splenic and portal vein have been outlined by percutaneous injection of contrast media directly into the substance of the spleen (From Leger, Albot, and Arvay Presse Méd, vol 59, 1951)

B and C Two portosplenic venograms contributed to this volume through the kindness of Louis M Rousselot, M D, New York City Both of these films were obtained by percutaneous injection of the spleen with the contrast medium In B is demonstrated the splenoportal coronary system of veins in a patient with cavernomatous transformation of the portal vein In C, a patient with typical intrahepatic block due to cirrhosis, the portal and splenic vessels are clearly demarcated

... extrahepatic portal

circulation can be visualized

components of this type of collateral circulation are the deep cholecystic veins, the epiploic veins of the gastric omentum, the hepatocolic and hepatorenal veins, and the accessory veins of Sappey.

Recently Edwards has reviewed the entire subject of communications between the portal and systemic circulations. In addition to confirming the observations of eighteenth century anatomists, this investigator discusses in detail the potential adequacy of these collaterals in portal venous obstruction He emphasizes particularly the functional importance of the anastomoses about the umbilicus, the spleen, the left kidney, and the rectum.

As interest in this syndrome has increased, a number of ingenious efforts have been made to develop refinements in diagnostic technique which would prove or disprove the presence of portal hypertension A few of these have been useful, but none has provided the diagnostic accuracy which is so badly needed For instance, Newman has developed an indirect method whereby circulation time from the rectum to the lungs is measured Here, ether is instilled into the rectum and timed for its appearance on the breath of the patient Bean has suggested a technique to measure pneumatically the pressure at which the sigmoidal mucosa blanches. A number of investigators have attempted to establish a diagnosis of portal hypertension by measuring the pressure in the distended abdominal veins so often seen in cirrhosis Various authors (Sherlock and Walshe, Billings and DePree, Bean and his associates; and Blondheim and Kunkel) have been able to show that certain sugars and proteins, after oral ingestion, appear earlier and in greater concentration in the dilated anterior abdominal veins than in the antecubital vein. Although most of these indirect methods have provided a pleasant clinical diversion, none of them has proved really useful.

At the present time, one technique in particular appears to hold promise This involves transperitoneal injection of a large amount of radio-opaque medium such as Diodrast directly into the spleen Shortly thereafter roentgenograms are obtained, and it is quite remarkable how clearly the splenic and portal vein can be identified. This technique, originally described by Abeatici and Campi, has been widely adopted In Figure 72A, B, C, D are reproduced four typical splenoportograms In connection with this technique, a note of warning is in order, percutaneous injection of the spleen in patients with elevated portal pressure may be followed by serious hemorrhage from the site of splenic puncture. It should not, therefore, be performed unless access to an operating room is immediately available

As emphasized previously, the most important clinical feature of

liberated from degenerating liver tissue The experiments do not exclude the possibility that the spleens enlarged in direct response to the carbon tetrachloride itself

In portal hypertension, the associated anemia, leukopenia, and thrombocytopenia have always proved a perplexing problem Since the hematological picture generally disappears following adequate portal decompression or splenectomy, it is generally accepted that the spleen is responsible for the abnormal blood picture The exact mechanism whereby splenomegaly produces these abnormalities in the peripheral blood is unknown, but they are believed to be due to hyperfunction of this organ For this reason, the currently popular use of the term "hypersplenism" is probably justified

Before leaving the subject of portal hypertension in man, an additional comment on a most interesting phase of this syndrome as it is seen clinically seems required This concerns a group of patients in whom the picture is confused by non-conformity Attention has been called to the fact that varices can apparently exist in the esophagus without either cirrhosis or extrahepatic block Furthermore, every series of patients suspected of, or proved to have, portal hypertension contains a few whose varices apparently recede and reappear intermittently Because the clinical picture, if indeed it exists at all, is so ill-defined, attention can perhaps be best focused upon it by a recitation of the following two case histories

> CASE 1 H C A twenty-eight-year old registered nurse who was married and the mother of two children first came under medical surveillance at the age of eighteen years At this time, admission to a training school for nurses was refused, because on routine phys [illegible] [illegible]ation she was found to have an enlarged spleen Late[illegible] [illegible] to another training school, [illegible]
> not so stringent [illegible]
> severe esophagogastric hemorrhage from [illegible] uneventfully X-rays demonstrated a small stomach ulcer Several years later, while on duty at another hospital, she had another severe hemorrhage Following this, a splenectomy was performed, and at the time the surgeon made the comment that her liver "appeared to be cirrhotic" A biopsy was not taken She was well for five years, and then again a massive hemorrhage appeared This time she was suspected of having a duodenal ulcer on the basis of two gastrointestinal series, but no varices could be demonstrated On roentgen examination of her esophagus after transfer to this hospital, however, varices were believed to be present She was operated upon and, although her liver grossly appeared to be the site of a minimal cirrhosis, the

r . . . . .

but the ...

shaped" radiolucent areas characteristic of varices ...
ing and the use of the Valsalva maneuver have been found useful in this clinic in demonstrating varicosities of the esophagus. The pattern of the normal gastric mucosa is so varied that varices in the cardia of the stomach are extremely difficult to detect. At the present time, the radiographic demonstration of esophagogastric varices is the single most important diagnostic procedure in establishing the presence of portal hypertension.

Splenomegaly, although common indeed in patients with portal hypertension, is by no means pathognomonic. Of the 1189 cases of splenomegaly studied by Whipple, additional evidence of portal hypertension was present in only 174 patients or 14 per cent of the ... were patients with anemia,

...

patients came to operation, and when ...
hepatic portal bed block was present, pressures ranged from 25 to ... cm. of saline. In patients without portal bed block, the pressure ranged from 7 to 29 cm. of saline. Although there is some overlap between these two groups, it is not significant. There was no evidence th... splenic enlargement influences portal pressure. Several ... in the pathogenesis of

splen...
... of the available evidence, ... also believes ...

the ...
ing the intensity of the splenic ...
the pressure. At present, it is generally accepted that the spleen enlarges and becomes fibrotic when subjected to abnormally high levels of pressure in the portal system, but there is some evidence th... other factors may be involved. For instance, Cameron has ob... ... that there may be some

rela...
arrived at this conclusion by transp... subcutaneous space, thereby effectively severing any connection ... this organ with the portal system. Sublethal hepatic necrosis was then induced by exposure to carbon tetrachloride. The splenic transplants consist... and whether they were associated with the portal or syst... from these experiments th... creases in portal ...

twenty-one, this man developed bouts of anemia lasting several months On one occasion, he was so severely anemic as to be thought in heart failure It was with this medical background that G M presented himself for treatment

Physical examination disclosed a pale but husky youth of twenty three years The only findings of importance were a large, non-tender liver palpable 6 cm below the right costal margin The spleen was enlarged 4 cm below the left costal margin

Laboratory Data Hemoglobin—8 7 grams, red blood count—2 88, white blood count—4500, platelets—327,000; polymorphonuclears—51 per cent, lymphocytes—41 per cent, monocytes—2, eosinophils—1 per cent, reticulytes—0 2 per cent Stools were repeatedly negative for occult blood

Roentgen studies were entirely negative although the enlargement of the liver and spleen were reflected in a plain abdominal film Esophagram failed to reveal evidence of varices

The hematologist's opinion was that this man's anemia could be explained upon the basis of blood destruction, and that this might be minimized by splenectomy

Operation Portal Venography, Measurement of Portal Pressure, and Splenectomy

The patient's abdomen was entered through a generous left paracostal incision. A convenient vein in the upper jejunal mesentery was catheterized and the portal pressure found to be 26 to 28 cm of saline A portal venogram demonstrated a normal portal vein and a hugely enlarged liver (Fig 86) The spleen was enlarged several fold but was not unusual in appearance The spleen was removed uneventfully

Pathological Diagnosis—Dr MacMahon

Spleen—"The pattern here has features in common with (a) thrombocytopenia purpura and (b) congenital hemolytic anemia"

Liver—"Pigment cirrhosis'

Lymph Node—"Benign reactive lymphadenitis"

Skin—"The picture is consistent with cutaneous hemosiderosis"

Postoperative Course This was uneventful There was a marked rise in the platelets to a peak level of 1,500,000 This fell to 950,000 by the time of discharge The white cells also rose to a peak of 17,700 and fell to 10,800 by the time of discharge

Discussion The evidence accumulated preoperatively and during operation proved that this man was suffering from portal hypertension due to a posthepatitic cirrhosis In response to this, the spleen had enlarged and produced signs and symptoms of

pathologist reported that, upon examination of a microscopic section, its structure was all but normal Pressure in the portal vein was 22 cm. of saline, and a portal venogram failed to reveal evidence of extrahepatic portal obstruction. There was no sign of varicosities in her coronary system. A shunt was not performed, and her postoperative recovery was quite uneventful. Extensive liver function tests failed to reveal evidence of impaired function. Postoperative esophagograms were normal

Here, then, is a young woman in whom few observations seem to fit together That she bled severely on several occasions is a matter of record Though her liver appeared abnormal to two surgeons over a ten-year period, the pathologist could not detect important abnormalities in a microscopic section. Her portal pressure, though not normal, was not sufficiently elevated to warrant the risks of portal decompression That she will bleed again seems likely. Certain of the complexities of this interesting case may be clarified if it be permissible to regard certain types of portal hypertension as intermittent Some support to this contention is found in a series of 4 patients currently reported by Dye and his associates. All of these individuals were followed either by roentgen visualization of their varices, by esophagoscopy, or by operation. The most interesting feature was that over a period of months, varices were observed to disappear In several patients with varices, operation failed to disclose any significant elevations in portal pressure. Apparently, then, there is a small number of patients in whom the course of portal hypertension may be intermittent Whether any significant number of such patients will be discovered, only time and detailed study will reveal When all the evidence available in a given case is reviewed with the purpose of making a diagnosis of portal hypertension, it probably must be stated that the last word is not said until the portal

nature

CASE 2 G M. A single male of twenty-three years was admitted to the hospital with a chief complaint of anemia. In chronological order, the important events of his illness are as follows·

At the age of five years he, as well as two siblings, were jaundiced for a period of five to six weeks. Recovery was considered complete

At the age of seventeen years, he sustained a large hematoma of his thigh as a result of a football injury A few months later, he was found to be severely anemic but responded to supportive treatment well Annually at the ages of nineteen, twenty, and

prove useful in the therapy of ascites, but it is not at all clear whether he or those who had the temerity many years ago to attempt the operation in man had any idea of actually lowering abnormally high levels of portal pressure Yet even these same men must have had some idea of lowering portal pressure For instance, the conviction had been expressed many times that ascites was due to congestion of the splanchnic veins How else could these men have conceived of the Eck fistula as a useful form of treatment except to relieve an elevated portal pressure? If it were possible to establish that congestion was synonymous with portal hypertension in the minds of these early scientists, many of these difficulties would be resolved No matter what conclusion to these perplexing problems is finally reached, the fact remains that a number of therapeutic efforts were directed toward clinical phenomena commonly associated today with portal bed block

dominal paracentesis was undoubtedly the first technique employed Who conceived the idea of plunging a hollow needle into the abdominal cavity to relieve the intolerable pressure caused by massive ascites is not known, but it is likely that this primitive form of treatment was a part of even the earliest systems of medicine Certainly it was commonly practiced during the eighteenth and nineteenth centuries Even at this time, it was recognized that except for temporary relief abdominal paracentesis accomplished little So poor were the results of this practice that it is not surprising that, as surgery began to come of age, some more permanent measure for the treatment of ascites should have been sought

From time to time, a number of physicians noted that as splanchnic venous congestion developed in patients with cirrhosis, nature herself attempted to afford relief through the formation of collaterals As a direct result of these observations several men, more or less simultaneously, conceived the idea of aiding nature in her efforts by creating collaterals between the splanchnic and systemic circulations Around 1900, Morison, Talma, and Drummond and Morison all proposed that were the omentum, an organ drained by the portal system, sutured to the abdominal wall, vascular adhesions would be created, these it was hoped would lead off an additional portion of the blood pooled in the splanchnic bed Interestingly enough, one of these early operations was designed not only to connect the portal with the systemic circulation, but also to improve the blood supply to the cirrhotic liver The small size of this organ in advanced cirrhosis was attributed by many of the early investi-

excessive blood destruction. The elevated portal pressure was not adequate, however, to have produced esophageal varices and attendant hemorrhage A normal portal vein, adequate for decompressive purposes, was demonstrated.

In view of these facts, splenectomy was considered the operative procedure of choice A splenorenal or portacaval shunt was not considered proper at this time, for neither had this man bled massively from his gastrointestinal tract nor was his pressure high enough to make this a reasonable possibility. Armed

most important in this man to have combined the splenectomy with a splenorenal shunt, for this would have been this man's only opportunity to have had, if the term be permissible, a satisfactory prophylactic portal decompression It is well known that the only time a splenorenal shunt can be performed is at the time of splenectomy If advantage is not taken of this opportunity, it is lost forever, for the splenic vein shrinks to proportions quite unsuitable for shunting purposes

Here, then, is a young man who, from the surgical point of view, developed portal hypertension secondary to cirrhosis of the liver It appears logical to ascribe the cirrhosis to his bout of infectious hepatitis His portal hypertension had not endangered his life directly, yet his hypersplenism had certainly provided a serious handicap to normal activity.

These two cases are of interest, not only for the details of their proper management, but also for their relationship to the problem of portal hypertension as a whole Although certain aspects of their clinical features must remain speculative, they do present certain important points for consideration. In the first, the portal hypertension undoubtedly fluctuated, while in the second, the hyperfunction of the spleen may be directly related to the portal hypertension As time goes on and more such cases are completely studied, portal hypertension will undoubtedly be found to have a broader clinical spectrum than is commonly appreciated today

TREATMENT

Historical

If it proves difficult to determine just when the concept of portal hypertension became established, it is even harder to decide just what should properly be regarded as the earliest form of treatment of this syndrome It is true that Eck suggested that his fistula might

dominal wall in such a fashion that fluid presumably could drain freely into the subcutaneous abdominal space In spite of a small number of reported successes with this technique, it was never very widely practiced

When it was demonstrated that patients with hemorrhage from varices could be protected from further hemorrhage by a portacaval shunt, it was logical that this operation should again be tried primarily for the relief of ascites The results were so disappointing that the operation for this condition was promptly dropped At the moment, ascites remains unconquered by surgery Whether or not ligation of the hepatic artery will prove useful in the treatment of ascites remains to be determined

Splenectomy enjoyed a relatively long period of popularity in the treatment of states now recognized to be due to portal hypertension As early as 1866, Spencer Wells removed the spleen for so-called splenic anemia In 1875 Péan reported that he had performed a splenectomy primarily to relieve the pain and discomfort caused by excessive enlargement of this organ As this operation as well as other major surgical procedures became safer, it was performed widely for a number of splenic disorders, and not an insignificant number were for Banti's disease Its use was also extended to splenomegaly associated with cirrhosis As experience accumulated in regard to these two clinical states which in many respects resemble each other, it became apparent that occasionally in Banti's disease all signs of anemia disappeared, and the patients were no longer troubled by hematemesis It also was noted that when cirrhosis complicated the picture, the results were uniformly poor In the light of what is known today of the pathological processes involved in these two states, it seems logical to assume that those patients with Banti's disease who responded so favorably were probably the rare individuals whose thrombosis was restricted to the splenic vein As a result of a rather wide experience with splenectomy in patients with what is recognized today as portal hypertension (Mayo, Pemberton, and Andrus and Holman), this operation came to be reserved for the young individual without associated stigmata of cirrhosis Because the underlying factors were not understood, the selection of cases was poor, and every reported series contained many more failures than successes

The generally poor record of both omentopexy and splenectomy served as a constant stimulus for the development of a better form of therapy for patients with splenic enlargement and bleeding varices In 1926 Flerow reported some success in preventing hematemesis by ligating the left gastric artery, the right and left gastrosplenic arteries, and the inferior mesenteric vein A few years later, Walters

gators to an inadequate blood supply. This aspect of the purpose of an omentopexy was soon lost, and as the operation came ultimately to be performed, its object was to encourage the development of collaterals between the portal and systemic circulations.

One or another variation upon the original Talma-Morison-Drummond operation was widely practiced during the early part of the century, but without very conspicuous success. Such famous surgeons such as Credé, Franke, Monprofit, and others reported their series of patients who had been subjected to this operation These men stated that complete relief of ascites could not be anticipated in more than 20 to 30 per cent. In retrospect, it seems unlikely that the small increase in collateral circulation established by the omental graft could have contributed importantly to this generally reported rate of cure In light of what is known about cirrhosis today, it appears more probable that those reported cured by omentopexy had merely passed into a relatively quiescent phase of their disease during which the formation of ascitic fluid was scant. At any rate, the results appeared so poor to Rosenstein that in 1912 this surgeon was prompted to try portal decompression by means of an Eck fistula.

As the inadequacies of omentopexy became more and more apparent, numerous efforts were made to relieve the ascites by diverting the abdominal fluid either into the systemic venous system or into one or another of the subcutaneous spaces immediately adjacent to the abdominal cavity. Perotte attempted to direct a flow of ascitic fluid into the central end of the divided saphenous vein To accomplish this, the opened vein was sutured directly to a small split in the abdominal peritoneum Evler and also Handley modified the technique by constructing a funnel of peritoneum Lambotte, Fauvel, Franke, and Rolleston among others devised various types of silk sutures, glass tubes, rubber tubes, and even steel rods, the common objective of all being to channel fluid from the peritoneal cavity into various adjacent subcutaneous spaces From these spaces it was hoped that the fluid would be absorbed into the general circulation All in all, a great many of these techniques were developed, tried, and discarded because none of them proved effective.

In addition, several other surgical maneuvers were devised, advocated, and in turn abandoned The spleen was split and implanted in the abdominal wall Both kidneys were decapsulated in the hope that they might provide an absorptive surface. But again convincing successes were never reported The urge to relieve ascites by some mechanical device has proved strong, and almost each decade has provided some new technique The most recent of these is the Crosby-Cooney button which enjoyed some measure of success a few years ago. The glass or plastic button was sutured into the ab-

some time in the past, the chances of performing a splenorenal shunt are virtually non-existent and under these circumstances, the portacaval shunt must be employed provided the portal vein has not been occluded by a thrombus In general, however, the portacaval shunt has been accepted as the most useful procedure in patients with cirrhosis. When the block lies outside the liver the splenorenal shunt is preferred, for the portal vein is frequently compromised by a thrombus and therefore useless for purposes of portal



[illegible] 4 A Varices of the [illegible] moderately advanced [illegible] splenorenal shunt for [illegible]

decompression Blakemore favors the portacaval variety of shunt because he feels that the portal vein is consistently of larger caliber than the splenic Rousselot, on the other hand, has long advocated the splenorenal shunt His chief reason for this preference lies in his belief that splenectomy should be a routine part of portal decompression In removing the spleen, the hypersplenism if it be present is promptly relieved, and in addition a considerable amount of blood is prevented from entering the portal system However, two factors might favor leaving the spleen in place, thus organ shrinks in size following adequate portacaval shunt, and the large collaterals between the spleen and lateral body wall are preserved In both types of shunt, the portal pressure is lowered to safe levels, and in so far as can be determined roentgenographically, the varices disappear

and his associates advocated ligation of the left gastric artery, and Blain was attracted to the idea of ligating the splenic artery. In 1933 Holman expressed the belief that ligation of the splenic artery together with splenopexy might be helpful In a recent article on portal hypertension by Gerbode and Holman, two patients were reported who had been well for over twelve years after this operation had been performed. The common objective in these operative procedures was, of course, to reduce the amount of blood actually gaining access to the portal venous bed.

In 1939 another form of therapy made its appearance. Crafoord and Frenckner devised a transesophageal endoscopic technique whereby varices in the esophagus could be injected with a sclerosing solution under direct vision They reported a number of successes and this procedure was widely practiced and for a time enthusiastically advocated by Moersch Although a number of good results were reported, the technique appeared too hazardous and the successes too meager to encourage American endoscopists to adopt the procedure very widely

Direct Portal Decompression

The modern era in the treatment of portal hypertension began in 1945 in this country In this year, Whipple and Blakemore and

mortality During the next eight years, a number of men showed repeatedly that after the successful establishment of a portacaval or splenorenal shunt, patients are protected against recurrent life-endangering hematemesis In addition, it has been proved that portal decompression by means of a portacaval shunt is also followed by shrinkage of the spleen and subsidence of the signs of hypersplenism provided these were present prior to operation. Experience to date with portal decompression is sufficiently extensive to warrant its discussion in some detail

That excessively high pressure in the portal venous system can be effectively lowered by either a portacaval or splenorenal shunt now is a matter of record The question of which one of these shunts is to be employed and just how it is to be fashioned is, however, a problem which is widely discussed and to which no completely satisfactory answer has as yet been obtained Each, under certain circumstances, has its own specific indications and contraindications For instance, it is well known that if the spleen has been removed

ment of portal hypertension must be prepared to perform whichever type of shunt is indicated by the situations arising during the course of the operation In addition, he should be prepared to insert an autogenous vein graft between the portal and systemic circulations ✓Occasionally, a patient will be encountered in whom a graft alone can be relied upon to decompress the portal system satisfactorily

In considering the portacaval shunt specifically, one problem remains unsolved should this be performed in the end to-side position or would a lateral or "false" Eck fistula be preferable? In the former, the liver is totally deprived of portal blood (Fig 74) In the latter, a mechanism is provided by which some portion of portal blood gains access to the liver Those who favor the side-to side shunt maintain that portal decompression is adequate and that it is good for some portal blood to enter the liver This contention is based on those experiments performed in the dog which prove that hepatic regeneration does not take place in the face of an Eck fistula In addition to facilitating regeneration, two additional facts derived from animal experiments provide theoretical evidence that the side-to-side shunt is preferable It has been shown that Bromsulphalein retention in dogs with an end to-side shunt is higher than in those with a shunt in the side-to-side position (Preshaw and associates) Furthermore, Harper and Gardner and their associates have demonstrated abnormalities of amino acid levels in peripheral blood in the presence of an end to-side shunt Whether these animal experiments are applicable to patients with cirrhosis has yet to be proved Certain it is that in The New York Hospital series of 30 portacaval shunts performed in the end-to-side position it has been impossible to identify untoward effects which could be ascribed to lack of portal blood reaching the liver

Those who favor the end to-side shunt believe that the resulting portal decompression is more effective when the shunt is performed in this position In addition, they believe that the objections to this type of shunt have been largely theoretical, and they point out that it is highly unlikely that any portal blood at all actually gains access to the liver through a "false" Eck fistula So high do they believe hepatic resistance to be in cirrhosis that hepatic blood flow may partially reverse itself In the presence of a side-to-side shunt, it is believed by some that a certain increment of portal blood may flow in retrograde fashion *from the liver, through the side-to side shunt,* and thence into the vena cava As yet, this hypothesis has not been ✓proved Of some practical importance in considering these two shunts is the fact that occasionally the caudate lobe may be so large as to preclude the approximation of the portal vein and vena cava

rather early in the postoperative course In Figure 73 are reproduced preoperative and postoperative esophageal roentgenograms, the latter obtained several weeks after a successful splenorenal shunt

At present, it is impossible to set any hard and fast rule by which to determine which type of shunt should be performed. The logical approach at present seems to be that a surgeon undertaking the treat-

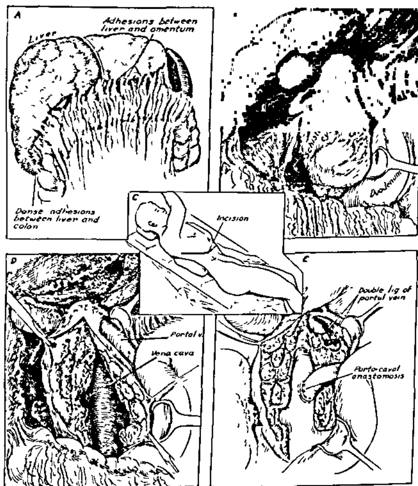


Fig 74 J M. N Y H #578,933 Diagrammatic representation of the operative findings and accomplishments in a patient with advanced schistosomiasis of the liver, portal hypertension, esophageal varices, and massive hematemesis Of particular interest was the large schistosomal cyst surrounding the vena cava This had to be split and partially resected to permit access to the vena cava before an end-to-side portacaval shunt could be fashioned.

a particularly serious issue. Today, removal of one kidney and an end-to-end anastomosis between the splenic and renal veins is rarely performed.

Another technical matter of some importance concerns the manner in which the end-to-side splenorenal shunt is carried out. Portal bed decompression can be satisfactorily attained either by occluding the renal artery or by partially occluding the renal vein with an appropriate clamp while the shunt is being constructed. It is probable

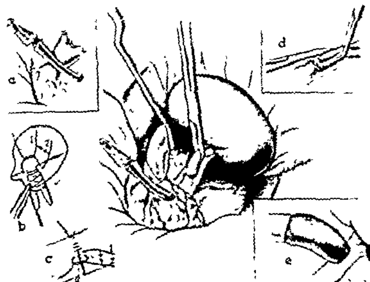


Fig. 76. In his extensive experience with splenorenal shunts Rousselot has demonstrated how greatly this valuable procedure may be facilitated by the use of an autogenous venous graft obtained from the superficial femoral vein. (From Rousselot: Surgery, vol. 31, 1952.)

that a slightly more efficient anastomosis can be performed with the renal blood flow completely stopped, yet it is still a matter of some concern that the kidney should be deprived of blood for a period of thirty to sixty minutes. This particular point, however, can probably be relegated to a position of minor importance.

A most important aspect of splenorenal anastomosis has been studied intensively by Rousselot who, like other investigators, has been frustrated by the difficulties met in dissecting free a segment of splenic vein satisfactory for anastomotic purposes. He proposed that the splenic vein be dissected back on the pancreas as far as necessary to obtain a large, healthy segment of vessel. The gap left, Rousselot proved, could be successfully bridged by an autogenous

in the side-to-side position Here, of course, the end-to-side shunt is technically much easier

When originally proposed, the splenorenal shunt presented a technical problem comparable with that which still exists in the portacaval Should the splenorenal shunt be performed end-to-end with renal vein, or would it not be possible and more advantageous to employ an end-to-side variety? In proposing the splenorenal shunt, Blakemore and Lord removed both the spleen and the left kidney

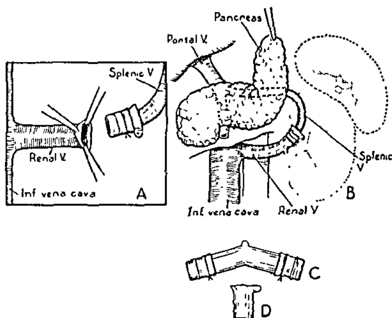


Fig 75. In Blakemore's original splenorenal shunt the kidney was removed and portal decompression obtained by an end to-end anastomosis between the splenic and renal veins (From Blakemore and Lord· Ann Surgery, vol 122, 1945)

and made an anastomosis between the distal end of the splenic vein and the proximal end of the renal vein (Fig. 75). However, at this time, they pointed out that sacrifice of the kidney was probably *unnecessary and that the splenic vein could in all probability be* easily sutured to the side of the renal vein. Linton, Rousselot and others have consistently deplored the removal of one kidney and [illegible] advocated that the splenorenal shunt always be performed in

this collected series includes many single case reports, the mortality figure obtained approximates that reported in some of the larger consecutive series of patients In Blakemore's series, there were 12 deaths in a series of 81 patients, a postoperative mortality of 14 per cent, Linton had 10 deaths in 56 cases, a mortality rate of 17 per cent In The New York Hospital series of 37 cases, there were 4 deaths, a mortality of 10 per cent Although this mortality rate is high, still it compares favorably with a number of other surgical procedures of comparable magnitude As technique improves and cases are selected more critically, it can be expected that this current figure may be reduced to even more acceptable levels

LATE RESULTS To date about 362 case reports of patients with venovenous shunts of one variety or another are available in the medical literature for study (Tables 4 and 5) Since only about 40 of these were reported prior to 1950, it is obvious that the follow-up studies are too short to permit any final evaluation of the effectiveness of portal decompression As, however, such material as is available is studied, it becomes apparent that, whenever an effective shunt has been performed and the portal pressure is dropped importantly, the patients are protected from recurrent massive hematemesis

Although the period of follow-up in our series of patients is short, a detailed study of these individuals has produced a number of interesting and instructive observations For this reason it is considered profitable to review this relatively small series in some detail At The New York Hospital, 37 shunts have been performed upon 36 patients, 30 of these were end-to-side portacaval anastomoses, 4 were end-to-side splenorenal, and in 1 patient a side-to-side portacaval shunt was employed In 2 instances, the superior mesenteric vein was used for purposes of decompression All but one of these patients had bled one or more times prior to operation In all, varices were demonstrated by one means or another The initial portal pressure in all but one patient in this series was 30 cm of saline or more, and many readings were considerably above this critical level Following operation, the pressure in all but two of the patients with portacaval shunts fell below the 30 cm level (Fig 77 A) No explanation was apparent for the two failures, #15 and #24 The first two splenorenal shunts failed to produce a satisfactory fall in portal pressure as did the two anastomoses in which it was necessary to use the mesenteric vein These four shunts, due to technical difficulties, were considered inadequate at completion of the operation Given a patent portal vein it is usually possible to obtain a gratifying fall in portal pressure

graft taken from the patient's superficial femoral vein This technique may save many hours of tedious dissection and undoubtedly provides the patient with a shunt of good size. Rousselot's original illustrations are reproduced in Figure 76 One precaution must be exercised in the use of a femoral vein graft; the valves must open in the direction of the blood flow! Autogenous femoral vein grafts are not restricted to splenorenal decompressive operations. Blakemore

out an available splenic vein may present a lacuna of blood in the neighborhood of the junction of the portal, splenic, and superior mesenteric veins This vascular pool, in a fair number of patients, can be connected to the vena cava by means of a vein graft

The Results of Venovenous Shunts in the Treatment of Portal Hypertension

IMMEDIATE RESULTS There can be little doubt but that effective portal decompression is obtained by means of either a portacaval or a splenorenal shunt After studying the reported cases of portal hypertension which have been subjected to a venovenous shunt, it is obvious that an impressive fall in portal pressure is obtained whenever it is possible to construct a satisfactory anastomosis between the portal and systemic circulations A decrease in portal pressure of 18 to 25 cm of saline is commonly obtained immediately after opening the shunt, on occasion this fall may amount to as much as 30 cm of saline Expressed in somewhat different terms, it is not at all unusual for a patient whose portal pressure at the beginning of the operation is in the neighborhood of 45 to 50 cm to obtain a decrease to 20 to 25 cm of saline upon completion of the shunt Interestingly enough, the amount of fall is not as significant clinically as is the level of pressure obtained after opening the shunt Blakemore, calling upon his wide experience in this field, has stated that all patients who have bled seriously from esophagogastric varices have had portal pressure in excess of 30 cm of saline If, therefore, a given patient's portal pressure at the completion of a portacaval or splenorenal shunt is 30 cm of saline or less, he can be assured with reasonable certainty that he will not experience another catastrophic hematemesis Although the evidence is indeed meager, it is nevertheless adequate to indicate that there are additional increments in fall during the first several postoperative months

The over-all postoperative mortality in the 362 cases which have been reported to date is 14 per cent (Tables 4 and 5) Although

Longmire 1950	Cirrhosis or extrahepatic thrombosis	7	0	0	7	2 well, 1 unchanged, 4 follow-up deaths
Reynolds and Southwick, 1951	Cirrhosis	2	1	50	1	Well, time not stated (Vein graft used)
Falor and Golings, 1951	Cirrhosis	2	0	0	2	Well, time not stated.
Gerbode and Holman, 1951	Cirrhosis	6	1	16.6	5	1 died 5 mos after operation 4 well 2 wks to 23 mos
Gerbode and Holman, 1951	Extrahepatic thrombosis	1	0	0	1	Well, 11 mos
Julian and Fildes, 1951	Cirrhosis	2	0	0	2	1 melena 9 mos after operation, lost to follow-up 1 well, time not stated
Julian and Fildes, 1951	Extrahepatic thrombosis	1	0	0	1	Well, 6 wks or more
Lazzari and Rack, 1951	Hepar lobatum	1	0	0	1	Well, time not stated
Linton, 1951	Cirrhosis	11	3	27.2	8	Well, 6 mos. to 6 (?) yrs
Linton, 1951	Extrahepatic thrombosis	4	0	0	4	Well to 6 (?) yrs
Blakemore, 1952	Cirrhosis	65	13	20	52	7 follow-up deaths, 45 well to 7 yrs

TABLE 4
PORTACAVAL SHUNTS

AUTHOR AND DATE	PRIMARY DISEASE	NUMBER OF CASES	MORTALITY		SURVIVORS	FOLLOW-UP
			Number	Per cent		
Vidal, 1910	Cirrhosis	1	0	0	1	Well, 3½ mos
Rosenstein, 1912	Cirrhosis	1	0	0	1	Well, 5 mos., though required paracentesis several times with decreasing frequency
Krestovsky, 1927	Cirrhosis	2	0	0	2	Well, 4 mos Two postop paracenteses (Superior mesenteric to vena cava)
Linton et al 1948	*Cirrhosis*	2	2	100	0	
Julian and Metcalf, 1949	Cirrhosis	1	0	0	1	No follow-up
Patton and Johnston, 1949	Banti's disease	1	0	0	1	Well, 2½ years
Pattison, 1949	Cirrhosis	10	1	10	9	*1 died 43 days* after operation 8 well to 15 mos
Santy and Marion, 1949	Cirrhosis	1	1	100	0	
Mulligan, 1949	Cirrhosis	2	0	0	2	Well, time not stated.

TABLE 5
SPLENORENAL SHUNTS

AUTHOR AND DATE	PRIMARY DISEASE	NUMBER OF CASES	MORTALITY		SURVIVORS	FOLLOW-UP
			Number	Per cent		
Divine, 1948	Cirrhosis	1	0	0	1	Well, time not stated
Linton et al 1948	Cirrhosis	3	1	33 3	2	Well, to 29 mos
Linton et al 1948	Extrahepatic *cirrhosis*	6	2	33 3	4	Well, 2 to 22 mos
Tanner, 1948	Cirrhosis	1	0	0	1	Well, time not stated
Mino et al 1948	Sarcoidosis	1	0	0	1	Well, 18 mos
Santy and *Marion, 1948*	*Cirrhosis*	4	0	0	4	Well, 3 to 13 mos
Santy and Marion, 1948	Banti's disease	3	0	0	3	Well, 3 to 6 mos
Postlethwaite et al 1950	Extrahepatic thrombosis	1	0	0	1	Well, time not stated
Longmire, 1950	Cirrhosis or extrahepatic thrombosis	8	0	0	8	2 well, 4 improved 2 follow-up deaths
Urlings, 1950	Cirrhosis	1	0	0	1	Well, time not stated

TABLE 4

PORTACAVAL SHUNTS (*Continued*)

AUTHOR AND DATE	PRIMARY DISEASE	NUMBER OF CASES	MORTALITY		SURVIVORS	FOLLOW-UP
			Number	Per cent		
Blakemore, 1952	Extrahepatic thrombosis	4	0	0	4	No follow-up deaths.
Large et al 1952	*Cirrhosis*	13	2	15.4	11	1 died 6 mos postop, 1 bled once, 8 well 6 to 22 mos, 1 died 13 mos postop
Walker, 1952	Cirrhosis	2	0	0	2	No follow-up
Walker, 1952	Extrahepatic thrombosis	1	0	0	1	No follow-up
Child, 1953	Cirrhosis	31	4	12.0	24	3 follow-up deaths at 3 yrs, 16 mos and 38 days.
Totals		174	28	16.8	146	
Cirrhosis Totals		156	28	17.9	128	
Extrahepatic Thrombosis Totals		18	0	0	18	

Nabatoff, 1952	Cirrhosis and splenomegaly	1	0	0	1	Well about 14 mos
Large et al 1952	Cirrhosis	1	0	0	1	Well, 30 mos
Large et al 1952	Extrahepatic thrombosis	1	0	0	1	Well, 11 mos
Rousselot, 1952	Cirrhosis	6	1	16 6	5	1 recurrent hematemesis, not repeated 3 well 4 to 12 mos
Child, 1953	Cirrhosis	1	0	0	1	Well, 2 yrs and 5 mos
Child, 1953	Extrahepatic thrombosis	3	0	0	3	1 bled again and was reoperated 1 shunt closed and was reoperated 1 well, 1 yr and 3 mos
Totals		188	24	13 2	164	
Cirrhosis Totals		105	15	14 3	90	
Extrahepatic Thrombosis Totals		74	9	13 8	65	
Other		1	0	0	1	
Unknown		8	0	0	8	

TABLE 5
SPLENORENAL SHUNTS (*Continued*)

AUTHOR AND DATE	PRIMARY DISEASE	NUMBER OF CASES	MORTALITY		SURVIVORS	FOLLOW-UP
			Number	Per cent		
Kennedy 1950	Cirrhosis	1	0	0	1	Well, 5 mos.
Linton, 1951	Cirrhosis	19	1	5 2	18	4 continued to bleed
Linton, 1951	Extrahepatic thrombosis	27	6	22 2	21	
Gerbode and Holman, 1951	Cirrhosis	3	1	33 3	2	Well, 11 to 22 mos
Gerbode and Holman, 1951	Extrahepatic *thrombosis*	1	0	0	1	Well, 11 mos
Julian and Fildes, 1951	Cirrhosis	12	0	0	12	Well to 9 mos.
Dunlap, 1952	Cirrhosis	2	0	0	2	Well, 7 mos or more
Blakemore, 1952	Cirrhosis	54	11	20 4	43	18 follow-up deaths, 25 *well to 6 (?) yrs*
Blakemore, 1952	Extrahepatic thrombosis	27	1	3 7	26	4 follow-up deaths, 22 well to 6 (?) yrs

norenal shunt, #2-W D , whose final pressure remained at 34 cm , bled once postoperatively at one year, the bleeding has not recurred #3-P R bled nine months after her anastomosis This was unexpected, since her portal pressure had been lowered to 23 cm of saline

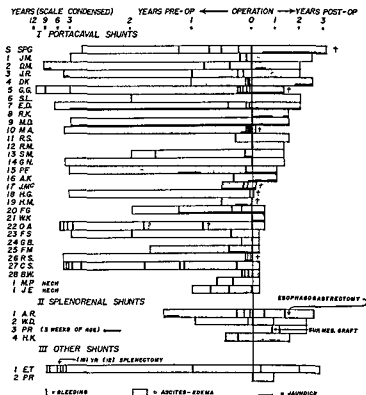


Fig 77 B This figure attempts to portray how the natural history of portal hypertension is altered by portal decompression To the left of the vertical line (operation) are recorded graphically the long-term preoperative features of each patient, to the right the postoperative results

as a result of her shunt On reexploration, the anastomosis was found to have closed The pressure had risen from 23 cm to 34 cm of saline Because a portacaval anastomosis in this patient was not technically feasible, a graft was employed between the superior mesenteric vein and the vena cava This superior mesenteric anastomosis,

The final pressure reading appears to correlate well with the subsequent clinical course of the patient in respect to recurrent hematemesis (Fig. 77 B) Only one patient in the portacaval series has bled postoperatively This patient (#4-D K) had a final pressure of 28 cm which is close to the critical level Her bleeding was a minor episode two years after her operation and was precipitated by a relapse to her former habits of alcoholism and food restriction. Three patients died in hepatic failure after leaving the hospital but did not bleed again P G , the first patient listed in the portacaval series, died after three years; #5, G G , died eighteen months post-

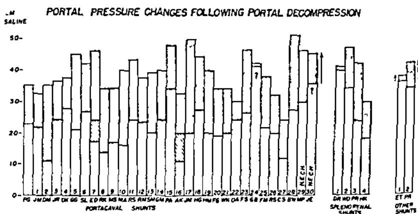


Fig 77 A In this figure the decreases in portal pressure following portal decompression are expressed graphically These represent measurements taken within ten to fifteen minutes after opening the shunt and probably do not represent the final level reached later in the postoperative course (see text).

operatively, and #17, J M C , thirty-eight days after leaving the hospital All but two portal pressure readings were well below the critical level of 30 cm of saline at completion of the operation None of these patients bled after portal decompression The two patients left with high portal pressure following operation, #15-P.F. and

pressures stabilized.

In the splenorenal series, the relationship of portal pressure to recurrent hematemesis is striking In neither of the first two patients

trol her recurrent hematemeses. The patient with the second sple

TABLE 6

DIAGNOSTIC ANALYSIS OF PREOPERATIVE AND POSTOPERATIVE ESOPHAGOGRAMS ON 37 PATIENTS WITH PORTAL DECOMPRESSION

TYPE SHUNT	CASE	PREOP	POSTOPERATIVE 1 MO	3 MOS	6 MOS	1 YR	2 YRS	3 YRS
PORTACAVAL SHUNTS								
S-S	0 PG	+	+	+	0	?	0	0/
E-S	1 JM	+	+					
E-S	2 DM	+					+	
E-S	3 JR	+	+		0		0	
E-S	4 DK	+	0			+	+	
E-S	5 GG	+	+				0/	
E-S	6 SL	+	+	+				
E-S	7 ED	?	+		0	0	0	
E-S	8 RK	0*				0	0	
E-S	9 MS	+	0		0		0	
E-S	10 MA	+	+/					
E-S	11 RS	+	+		0	0	0	
E-S	12 RM	+	+					
E-S	13 VM	+		0	0	0		
E-S	14 GN	+		0	0	0		
E-S	15 PF	+		0	0	0		
E-S	16 AK	+	0	0		0		
E-S	17 JMc	+		/				
E-S	18 HG	+	/					
E-S	19 HM	+	/					
E-S	20 EG	+		0				
E-S	21 WK	+	+	0				
E-S	22 OA	+						
E-S	23 FS	+	+					
E-S	24 GB	+						
E-S	25 FM	+						
E-S	26 RS	?	/					
E-S	27 CS	+	+					
E-S	28 BW	+	0					
E-S	29 MP (NECH)	+						
E-S	30 JE (NECH)	+						
SPLENORENAL SHUNTS								
	1 DR	+	+		+	+	+ +	
	2 WD	+	0				+	
	3 PR	+	+		+	+	+	
	4 HK	+		0	0	0		
OTHER SHUNTS								
	1 ET	+		+	+	+	+	+
	2 PR	+			+	+		

S-S = Side-to-Side
E-S = End-to-Side
+ = Varices Present
* = Positive Esophagoscopy
/ = Death
0 = Varices Absent

listed as #2-P R, was technically unsatisfactory and resulted in an actual increase in portal pressure to 36 cm of saline The patient states that since then, she has had some minor bleeding episodes These, however, have not been confirmed by the staff and are, therefore, open to question The other superior mesenteric shunt, #1-E.T, also had a small increase in pressure following the completion of his anastomosis and was left with a final reading of 38 cm of saline It is not surprising that this patient has subsequently bled again On two occasions, it was necessary to control his bleeding by use of the esophageal balloon

It is apparent, then, from these data that patients in whom an effective decrease in portal pressure was obtained have not bled again Most patients with borderline pressures, that is, in the neighborhood of 30 cm or so, or in whom portal pressure was not substantially reduced below this level, have suffered recurrence of hemorrhage. Furthermore, it is obvious, on consideration of the three deaths from parenchymal liver failure, that the portacaval anastomosis, while effectively lowering the pressure in the portal bed, does not materially affect the progressive course of cirrhosis

The clinical results of portal decompression and the final pressure reading obtained at operation correlate well with the information obtained from esophagograms performed at intervals during the postoperative period of follow-up (Table 6). Resolution of the pattern of esophageal varices occurred by the end of six months in every patient in the portacaval series None of these patients has bled again. In patient #4-D K, varices have reappeared and have been visualized on films obtained one and two years after operation. This is the one patient of the series with a portacaval anastomosis who has bled postoperatively This patient, as well as #2-D M, who also showed varices at two years, started to drink again, and both have failed clinically as evidenced by recurrent jaundice and edema. Varices have not reappeared in any other patients in the portacaval series

The correlation between the x-ray examination of the esophagus and the other criteria used to evaluate the adequacy of portal decompression is even more striking in the splenorenal and superior mesenteric series of shunts In the splenorenal group, numbers 1, 2, and 3 have all bled postoperatively, and all have shown persistence of varices on serial esophagograms. It will be recalled that in #1 and #2 the pressure was not lowered by operation, and in #3 the shunt thrombosed. This patient had a recurrence of portal hypertension and hematemesis The only patient with a successful splenorenal shunt, #4-H K, had a final pressure of 18 cm. of saline This patient has shown resolution of varices on repeated esophagograms and has enjoyed a benign clinical course (Fig. 73). In the case of the two

TABLE 6

DIAGNOSTIC ANALYSIS OF PREOPERATIVE AND POSTOPERATIVE ESOPHAGOGRAMS ON 37 PATIENTS WITH PORTAL DECOMPRESSION

PORTACAVAL SHUNTS

TYPE SHUNT	CASE	PREOP	POSTOPERATIVE 1 MO	3 MOS	6 MOS	1 YR	2 YRS	3 YRS
S-S	0 PG	+	+	+	0	?	0	0/
E-S	1 JM	+	+					
E-S	2 DM	+					+	
E-S	3 JR	+	+		0		0	
E-S	4 DK	+	0			+	+	
E-S	5 GG	+	+				0/	
E-S	6 SL	+	+	+				
E-S	7 ED	?	+		0	0	0	
E-S	8 RK	0*				0	0	
E-S	9 MS	+	0		0		0	
E-S	10 MA	+	+/					
E-S	11 RS	+	+		0	0	0	
E-S	12 RM	+	+					
E-S	13 SM	+		0	0	0		
E-S	14 GN	+		0	0	0		
E-S	15 PF	+		0	0	0		
E-S	16 AK	+	0	0		0		
E-S	17 JMc	+		/				
E-S	18 HG	+	/					
E-S	19 HM	+ /						
E-S	20 EG	+		0				
E-S	21 WA	+	+	0				
E-S	22 OA	+						
E-S	23 FS	+	+					
E-S	24 GB	+						
E-S	25 FM	+						
E-S	26 RS	? /						
E-S	27 CS	+	+					
E-S	28 BW	+	0					
E-S	29 MP (NECH)	+						
E-S	30 JE (NECH)	+						
SPLENORENAL SHUNTS								
	1 DR	+	+		+	+	+ +	
	2 WD	+	0				+	
	3 PR	+	+		+	+	+	
	4 HK	+		0	0	0		
OTHER SHUNTS								
	1 ET	+		+	+	+	+	+
	2 PR	+			+	+		

S-S = Side to Side
E-S = End to Side
+ = Varices Present
* = Positive Esophagoscopy
/ = Death
0 = Varices Absent

listed as #2-P R., was technically unsatisfactory and resulted in an actual increase in portal pressure to 36 cm. of saline. The patient states that since then, she has had some minor bleeding episodes These, however, have not been confirmed by the staff and are, therefore, open to question The other superior mesenteric shunt, #1-E T , also had a small increase in pressure following the completion of his anastomosis and was left with a final reading of 38 cm. of saline It is not surprising that this patient has subsequently bled again On two occasions, it was necessary to control his bleeding by use of the esophageal balloon

It is apparent, then, from these data that patients in whom an effective decrease in portal pressure was obtained have not bled again Most patients with borderline pressures, that is, in the neighborhood of 30 cm. or so, or in whom portal pressure was not substantially reduced below this level, have suffered recurrence of hemorrhage Furthermore, it is obvious, on consideration of the three deaths from parenchymal liver failure, that the portacaval anastomosis, while effectively lowering the pressure in the portal bed, does not materially affect the progressive course of cirrhosis

The clinical results of portal decompression and the final pressure reading obtained at operation correlate well with the information obtained from esophagograms performed at intervals during the postoperative period of follow-up (Table 6). Resolution of the pattern of esophageal varices occurred by the end of six months in every patient in the portacaval series None of these patients has bled again In patient #4-D.K , varices have reappeared and have been visualized on films obtained one and two years after operation. This is the one patient of the series with a portacaval anastomosis who has bled postoperatively This patient, as well as #2-D.M , who also showed varices at two years, started to drink again, and both have failed clinically as evidenced by recurrent jaundice and edema. Varices have not reappeared in any other patients in the portacaval series

The correlation between the x-ray examination of the esophagus and the other criteria used to evaluate the adequacy of portal decompression is even more striking in the splenorenal and superior mesenteric series of shunts In the splenorenal group, numbers 1, 2, and 3 have all bled postoperatively, and all have shown persistence of varices on serial esophagograms It will be recalled that in #1 and #2 the pressure was not lowered by operation, and in #3 the shunt thrombosed. This patient had a recurrence of portal hypertension and hematemesis The only patient with a successful splenorenal shunt, #4-H K, had a final pressure of 18 cm of saline This patient has shown resolution of varices on repeated esophagograms and has enjoyed a benign clinical course (Fig 73). In the case of the two

TABLE 8

DIAGNOSTIC ANALYSIS OF PREOPERATIVE AND POSTOPERATIVE SERUM GLOBULIN DETERMINATION ON 37 PATIENTS WITH PORTAL DECOMPRESSION

(Grams Per 100 ml)

TYPE SHUNT	CASE	PREOP	POSTOPERATIVE 1 MO	3 MOS	6 MOS	1 YR	2 YRS	3 YRS
PORTACAVAL SHUNTS								
S-S	0 PG	23	2.7	33	19	31	26 33 /	
E-S	1 JM	31	32					
E-S	2 DM	32	44			40	29	
E-S	3 JR	28	2.1		36			
E-S	4 DK	28	21		29	29	41	
E-S	5 GG	21	26	31	38	/		
E-S	6 SS	17	18	23		23	20	
E-S	7 ED	29	29			23 37		
E-S	8 RK	38	28	35		30 38		
E-S	9 MS	30	39					
E-S	10 MA	22 /						
E-S	11 RS	26	31	23		21 24		
E-S	12 RM	25	3.2					
E-S	13 SM	37	40			2.9		
E-S	14 GN	36	34		41	47		
E-S	15 PF	23	27		23 37			
E-S	16 AK	24	17	23	20 29			
E-S	17 JMc	29	38 /					
E-S	18 HG	24 30/						
E-S	19 HM	36 /						
E-S	20 FG	27	21	21				
E-S	21 WK	31	32	41				
E-S	22 OA	35						
E-S	23 FS	34	31					
E-S	24 GB	31	38					
E-S	25 FM	24						
E-S	26 RS	44 /						
E-S	27 CS	25	24					
E-S	28 BW	34	31					
E-S	29 MP (NECH)	28						
E-S	30 JE (NECH)	30						
SPLENORENAL SHUNTS								
E-S	1 DR	21	20	22		21	22	
	2 WD	23		20		29		
	3 PR	29	18	23		26		
	4 HK	31		35		4.2		
OTHER SHUNTS								
	1 ET	27	24		32	32	29	
	2 PR	25	24		28			

S-S = Side-to-Side
E-S = End to-Side
/ = Death

TABLE 7

DIAGNOSTIC ANALYSIS OF PREOPERATIVE AND POSTOPERATIVE SERUM ALBUMIN DETERMINATION ON 37 PATIENTS WITH PORTAL DECOMPRESSION

(Grams Per 100 ml.)

TYPE SHUNT	CASE	PREOP	POSTOPERATIVE 1 MO.	3 MOS	6 MOS.	1 YR	2 YRS.	3 YRS.
PORTACAVAL SHUNTS								
S-S	0 PG	41	35	38	41	52	37	2.8/
E-S	1 JM	47	37					
E-S	2 DM	41	31			34	40	
E-S	3 JR	43	30		42			
E-S	4 DK	42	38		49	57	34	
E-S	5 GG	40	32	31	36	/		
E-S	6 SL	44	42	46		45	44	
E-S	7 ED	41	40	40		37	36	
E-S	8 RK	47	31	47		42	59	
E-S	9 MS	42	39	26		51	42	
E-S	10 MA	34 /						
E-S	11 RS	47	46	43		38	47	
E-S	12 RM	41	42					
E-S	13 SM	35	36			54		
E-S	14 GN	44	35		27	41		
E-S	15 PF	42	43		41	52		
E-S	16 AK	33	40	35		33		
E-S	17 JMc	42	35/					
E-S	18 HG	36 23/						
E-S	19 HM	33 /						
E-S	20 FG	38	42	51				
E-S	21 WK	34	33	34				
E-S	22 OA	27						
E-S	23 FS	40	33					
E-S	24 GB	38	43					
E-S	25 FM	35						
E-S	26 RS	24 /						
E-S	27 CS	55	45					
E-S	28 BW	28	31					
E-S	29 MP (NECH)	38						
E-S	30 JE (NECH)	37						
SPLENORENAL SHUNTS								
	1 DR	42	41		47	47	44	
	2 WD	57	66			51		
	3 PR	48	42		50	47		
	4 AK	38		33		37		
OTHER SHUNTS								
	1 ET	48	43			48	54	
	2 PR	43	45	48	55			

E-S = End-to-Side
S-S = Side to-Side
/ = Death

TABLE 8

DIAGNOSTIC ANALYSIS OF PREOPERATIVE AND POSTOPERATIVE SERUM GLOBULIN DETERMINATION ON 37 PATIENTS WITH PORTAL DECOMPRESSION

(Grams Per 100 ml.)

PORTACAVAL SHUNTS

TYPE SHUNT	CASE	PREOP	POSTOPERATIVE 1 MO	3 MOS	6 MOS	1 YR.	2 YRS	3 YRS
S-S	0 PG	23	27	33	19	31	26 33 /	
E-S	1 JM	31	32					
E-S	2 DM	32	44			40	29	
E-S	3 JR	26	21		56			
E-S	4 DK	28	23		29	29	41	
E-S	5 GG	21	26	31	38	/		
E-S	6 SL	17	18	23		23	20	
E-S	7 ED	29	29			23 37		
E-S	8 RK	18	26	55		30 38		
E-S	9 MS	50	39					
E-S	10 MA	22 /						
E-S	11 RS	26	31	23		31 24		
E-S	12 RM	25	32					
E-S	13 SM	37	40			29		
E-S	14 CV	36	54		41	47		
E-S	15 PF	23	27		23 37			
E-S	16 AK	24	17	25	20 29			
E-S	17 JMc	29	38 /					
E-S	18 HG	24 30/						
E-S	19 HM	34 /						
E-S	20 FG	27	21	21				
E-S	21 WK	31	32	41				
E-S	22 OA	35						
E-S	23 FS	34	33					
E-S	24 GB	33	38					
E-S	25 FM	24						
E-S	26 RS	44 /						
E-S	27 CS	25	24					
E-S	28 BW	34	31					
E-S	29 MP (NECH)	28						
E-S	30 JE (NECH)	30						
SPLENORENAL SHUNTS								
E-S	1 DR	21	20	22		21	22	
	2 WD	23		20		29		
	3 PR	29	18	23		26		
	4 HK	31		35		42		
OTHER SHUNTS								
	1 ET	27	24		32	32	29	
	2 PR	25	24		28			

S-S = Side-to-Side
E-S = End-to-Side
/ = Death

TABLE 9

DIAGNOSTIC ANALYSIS OF PREOPERATIVE AND POSTOPERATIVE
ALKALINE PHOSPHATASE DETERMINATION ON 37 PATIENTS WITH PORTAL DECOMPRESSION

PORTACAVAL SHUNTS

TYPE SHUNT	CASE	PREOP	POSTOPERATIVE 1 MO	3 MOS	6 MOS	1 YR	2 YRS	3 YRS
S-S	0 PG	7 3			17	15	15 2	/
E-S	1 JM	10 4	25 8	16 3				
E-S	2 DM	4 8	6 6		10 6	9 3		
E-S	3 JR	9 7	5 2	8 7	12 8			
E-S	4 DK	6 8		3 5	19 2	8 8		
E-S	5 GG			9 8		/		
E-S	6 SL	2 6			4 6			
E-S	7 ED	33 6	63 5			21 2	13 9	
E-S	8 RK	7 4	7 0					
E-S	9 MS	18 0	28					
E-S	10 MA	3 8 6/						
E-S	11 RS	4 1	3 9	3 6		2 6	3 9	
E-S	12 RM	6 3	8 0					
E-S	13 SM	10 1	6 8					
E-S	14 GN	21 7	47 7		44 6			
E-S	15 PF	6 4	3 0		4 6			
E-S	16 AK	4 0	5 5	8 9	6 4			
E-S	17 JMc	8 9	6 9 /					
E-S	18 HG	5 3 8 7/						
E-S	19 HM	5 0 /						
E-S	20 FG	10 0	10 5	13 5				
E-S	21 WK	15 2	14 1					
E-S	22 OA	2 3						
E-S	23 FS	3 5	2 3					
E-S	24 GB	5 4	4 7					
E-S	25 FM	6 0						
E-S	26 RS	4 6 /						
E-S	27 CS	3 3	3 4					
E-S	28 BW	4 2	4 4					
SPLENORENAL SHUNTS								
	1 DR		7 5		11	4 6		
	2 WD	5 6						
	3 PR	6 0	10 4		6 3			
	4 HK	3 7	3 7					
OTHER SHUNTS								
	1 ET	3 8						
	2 PR	6 3	8 1		7 1			

S-S = Side-to-Side
E-S = End-to-Side
/ = Death

TABLE 10

DIAGNOSTIC ANALYSIS OF PREOPERATIVE AND POSTOPERATIVE SERUM BILIRUBIN DETERMINATION ON 37 PATIENTS WITH PORTAL DECOMPRESSION

(Milligrams Per 100 ml.)

PORTACAVAL SHUNTS

TYPE SHUNT	CASE	PREOP	POSTOPERATIVE 1 MO	3 MOS	6 MOS	1 YR	2 YRS	3 YRS
S-S	0 PG	11	11		37	27	25	21/
E-S	1 JM	1	31	11				
E-S	2 DM	7	35	16		12	14	
E-S	3 JR	12	17	11	8			
E-S	4 DK	3	2	6	35	11	40	
E-S	5 GG	23	27	197	63	/		
E-S	6 SL	1	5		10	10	7	
E-S	7 ED	60	87			141	113	
E-S	8 RK	24	23	15		7	46	
E-S	9 MS	41	210	238	73	47	40	
E-S	10 MA	25 /						
E-S	11 RS	7	18	10		14	17	
E-S	12 RM	14	10					
E-S	13 SM	8	16			11		
E-S	14 GN	37	90	65		52		
E-S	15 PF	13	90	21	22			
E-S	16 AK	12		22	120	18 26		
E-S	17 JMc	26	150 /					
E-S	18 HG	8 21/						
E-S	19 HM	10 /						
E-S	20 FG	21	43	36				
E-S	21 WK	14		40				
E-S	22 OA	9						
E-S	23 FS	16	28					
E-S	24 GB	13	47					
E-S	25 FM	27						
E-S	26 RS	135 /						
E-S	27 CS	3	7					
E-S	28 BW	17	46					
E-S	29 MP (NECH)	8						
E-S	30 JE (NECH)	16						
SPLENORENAL SHUNTS								
E-S	1 DR		5				5	
E-S	2 WD	6				4		
E-S	3 PR	3	1		5			
E-S	4 HK	8				12		
OTHER SHUNTS								
	1 ET	12	12				11	
	2 PR	5	4		6			

S-S = Side-to-Side
E-S = End-to-Side
/ = Death

TABLE 11

DIAGNOSTIC ANALYSIS OF PREOPERATIVE AND POSTOPERATIVE CEPHALIN FLOCCULATION DETERMINATION ON 37 *PATIENTS WITH PORTAL DECOMPRESSION*

PORTACAVAL SHUNTS FLOCCULATION UNITS*

TYPE SHUNT	CASE	PREOP	POSTOPERATIVE 1 MO	3 MOS	6 MOS	1 YR	2 YRS	3 YRS
S-S	0 PG	7	3	3	3	15	9	++++/
E-S	1 JM	3	15	4				
E-S	2 DM	16	18	15		++++		
E-S	3 JR	13	9	7	3		----	
E-S	4 DK	2	3			5		
E-S	5 GG	17				/		
E-S	6 SL	4	3			6		
E-S	7 ED	20				16		
E-S	*8 RK*	*4*	*9*	*10*	*7*	*9*	++++	
E-S	9 MS	16	21	++++		++		
E-S	*10 MA*	*11 /*						
E-S	11 RS	8	10	11	14			
E-S	12 RM	4						
E-S	13 SM	9						
E-S	14 GN	17	16					
E-S	15 PF	8	14		7			
E-S	16 AK	6		13	3			
E-S	*17 JMc*	*17*	+/					
E-S	18 HG	12 13/						
E-S	19 HM	20 /						
E-S	20 FG	11	*10*	*10*				
E-S	21 WK	14	2.1					
E-S	22 OA	+++						
E-S	23 FS	14	12					
E-S	24 GB	7	*0*					
E-S	25 FM	14						
E-S	26 RS	11 /						
E-S	27 CS	1	7					
E-S	28 BW	11	11					
SPLENORENAL SHUNTS								
	1 DR	6	4		0			
	2 WD	5			5			
	3 PR	10			5			
	4 HK	11						
OTHER SHUNTS								
	1 ET	3	6		7			
	2 PR	5	13		11			

S-S = Side-to-Side
E-S = End to-Side
/ = *Death*

* *0* — 0-4 units
+ — 5-9 units
++ — 10-14 units
+++ — 15-19 units
++++ — 20 + units

TABLE 12

DIAGNOSTIC ANALYSIS OF PREOPERATIVE AND POSTOPERATIVE THYMOL TURBIDITY DETERMINATION ON 37 PATIENTS WITH PORTAL DECOMPRESSION

PORTACAVAL SHUNTS   TURBIDITY UNITS

TYPE SHUNT	CASE	PREOP	POSTOPERATIVE 1 MO	3 MOS	6 MOS	1 YR	2 YRS	3 YRS
S-S	0 PG	3	3					/
E-S	1 JM	3	4					
E-S	2 DM	9					3 8	
E-S	3 JR							
E-S	4 DK	2					3 0	
E-S	5 GG	6	12	10		2 0/		
E-S	6 SL	2						
E-S	7 ED	6	8					
E-S	8 RK	4	3			1		
E-S	9 MS	16	11	16	11	11		
E-S	10 MA	10/						
E-S	11 RS	5	8	3		2 2		
E-S	12 RM	8	4					
E-S	13 SM	8	1 5			1 5		
E-S	16 AK	1	4	3	2	2 0		
E-S	17 JMc	5		9 /				
E-S	18 HG	3 5 0/						
E-S	19 HM	/						
E-S	20 FG	3		10				
E-S	21 WK	3	3	3				
E-S	22 OA	1 5						
E-S	23 FS	11	8					
E-S	24 GB	4						
E-S	25 FM	4						
E-S	26 RS	1 /						
E-S	27 CS	2	1					
E-S	28 BW	6						
SPLENORENAL SHUNTS								
	1 DR	4	3		1	1	.9	
	2 WD	2				8		
	3 PR	4	1		2			
	4 HK	6	5					
OTHER SHUNTS								
	1 ET	2	2			1		
	2 PR	2	4		6 6			

S-S = Side-to-Side
E-S = End-to-Side
/ = Death

patients with superior mesenteric shunts *in whom the portal pressure* was not reduced nor was further bleeding prevented, the esophagograms have continued to show large and extensive varices.

An additional point of significance arises from a consideration of the serial esophagograms (Table 6) In the portacaval series, all patients studied at six months have shown *a normal esophageal pattern* This includes #15 who failed to show an immediate decrease in por
three
of vari
ment in portal pressure may be a gradual one over a three-to-six month period rather than an abrupt change as reflected in the pres-

plore #16–A K, *two months after the completion of her portacaval shunt.* The portal pressure had been lowered by the portal decompression from 32 cm. to 20 cm of saline. At the time of her reexploration, the portal pressure had fallen further, 9 cm. of saline, below her post-shunt level and had stabilized at 11 cm of saline A similar slow adjustment may account for the change in the esophagogram of #15–P F, who was left with a portal pressure of 34 cm. at the completion of his portacaval anastomosis but who has had negative esophagograms at three, six, and nine months. This patient has not bled since his operation

Because the end-to-side portacaval shunt has been criticized on *the basis that it may seriously impair liver function, detailed charts* of selected preoperative and postoperative liver function test for The New York Hospital shunt series are reproduced in Tables 7–12 It will be noted that in this series, preoperative albumin levels are fairly high for the average case of cirrhosis (Table 7) This is due to careful selection and to concentrated supportive therapy before operation Within the month following operation, the average level of albumin in this series falls about 1 mg per 100 cc. despite continued dietary attempts to maintain it at the preoperative level By three to six months postoperatively, *most of the patients have regained* and are able to maintain their original albumin levels The *only patient in this group* whose albumin has fallen appreciably is
#-
Th

levels was found when serum bilirubin levels were determined serially (Table 10). During the first month after operation the bilirubin rose slightly, and then over the course of the succeeding three to six

months stabilized at its preoperative level In addition, all patients who were clinically jaundiced before operation continued to be so during their postoperative period #14–G N, and #9–M S, are excellent examples of this phenomenon The one patient in this series with biliary cirrhosis was jaundiced before operation and had long suffered from cutaneous pruritus and pigmentation These were unchanged by portal decompression The increase in bilirubin to 19 mg per 100 ml at three months in #5–G G appeared to be due to a fairly sharply defined episode of homologous serum jaundice

The globulins are of interest in that they consistently rise during the period of follow-up This may be interpreted as a reflection of the slow progression of the cirrhotic process which was not stayed by the portal decompression The cephalin flocculation and the thymol turbidity do not fit into any particular pattern The alkaline phosphatase rose in 4 cases (Table 9) This may possibly be due to regeneration of liver tissue The high levels of alkaline phosphatase recorded for #14 and #7 are thought merely to reflect the primary condition, advanced biliary cirrhosis in its obstructive phase (The function of the cirrhotic liver in the human, it would appear from this survey, is not altered appreciably by shunting portal blood away from the liver The function of the liver is certainly not improved by portal decompression, but, on the other hand, this operation is not followed by any important deviation from the predicted natural history of the disease)

(Certain aspects of the clinical course of patients with portal decompression are worthy of note Patients with jaundice preceding a shunt appear to be particularly prone to become more deeply jaundiced in the postoperative period The same is true of sodium and water retention as manifested by ascites and edema Most of these water-logged patients accumulated their fluid in the immediate postoperative period but were able to handle salt and water adequately three to six months after discharge from the hospital Patients who developed fluid after an episode of hematemesis also seemed to recover the ability to regulate their sodium balance quite easily and responded to conservative therapy within a short period of time Those patients, however, with a long history of ascites and edema unassociated with any one sudden demand on liver function were probably just getting by on extremely low levels of hepatic reserve In all probability, this was never quite adequate to meet the requirements of normal living Such patients were unable to handle sodium or water any better after their operation than before

There were 7 deaths in The New York Hospital series, 3 of liver failure at three years, sixteen months, and thirty-eight days respectively Autopsy on the first two of these patients revealed fully patent

TABLE 13

OTHER OPERATIONS ON EXTRAHEPATIC CIRCULATION

AUTHOR AND DATE	PRIMARY DISEASE	NUMBER OF CASES	OPERATION	MORTALITY		SURVIVORS	FOLLOW-UP
				Number	Per cent		
Socin, 1883	Ca of pancreas (1 Case had in addition ca of stomach)	2	1 Pancreas & gastric resection with ligation of hep art (*1* case had in addition ligation of gastric, gastroepiploic, & *pancreaticoduodenal* arteries)	2	100	0	
Salzer, 1889	Ca of pylorus	1	Ligation hep art & resection	1	100	0	
Bakes, 1889	?	1	Cholecystectomy & ligation hep art	0	0	1	Well in 2 wks
Kehr, 1903	Intrahepatic aneurism	1	Ligation hep art (hepatopexy)	0	0	1	Well, 1¾ yrs
Narath, 1904	Tumor, pancreas & stomach	1	Resection pancreas & *stomach with ligation*, hep art.	1	100	0	
Tuffier, 1909	Aneurism	1	Ligation hep art	1	100	0	

Villard & Tabernier, 1909	Cirrhosis	1	Sup mesenteric to rt ovarian	1	100	0	
Bogoras, 1913	Cirrhosis	1	Sup mesenteric to rt ovarian	0	0	1	
Kading, 1919	Intrahepatic aneurism	1	Ligation hep art	0	0	1	Well over 3 yrs
Colmers, 1921	Intrahepatic aneurism	1	Ligation hep art	0	0	1	Well time not stated
Everson and Cole, 1948	Cirrhosis	2	Ligation splenic art Omentopexy	0	0	2	Well, time not stated
Everson and Cole, 1948	Thrombosis splenic vein	1	Ligation splenic art Omentopexy	1	100	0	Died 1 mo postop
Phemister and Humphreys, 1947	Banti's disease	2	Esophagogastrectomy	0	0	2	1 bled 8 mos & 2 yrs postop 1 well 3½ mos & over
Linton, 1948	Banti's disease	1	Inf mesenteric to left adrenal	0	0	1	Continues to bleed
Linton, 1948	Cirrhosis	1	Inf mesenteric to vena cava	1	100	0	
Linton, 1948	Extrahepatic thrombosis	3	Inf mesenteric to vena cava	0	0	3	2 well, 13 & 22 mos 1 bled in 4 mos

TABLE 13

OTHER OPERATIONS ON EXTRAHEPATIC CIRCULATION (*Continued*)

AUTHOR AND DATE	PRIMARY DISEASE	NUMBER OF CASES	OPERATION	MORTALITY		SURVIVORS	FOLLOW-UP
				Number	Per cent		
Leger, 1950	Cirrhosis	1	Inf mesenteric to inf branch of renal	0	0	1	*Hematemesis 14 mos post-*op, well 21 mos
Purcell, 1950	Portal thrombosis	1	Sup mesenteric to vena cava	0	0	1	Tarry stool, 4 wks postop, well 8 mos +
Schafer and Kittle, 1950	Banti's disease	5	Esophagogastrectomy	0	0	5	1 bled once postop 5 well, short follow-up, time not stated
Schafer and Kittle, 1950	Cirrhosis	1	*Esophagogastrectomy*	0	0	1	
Gray and Whitesell, 1950	Cirrhosis	3	Devascularization of lower end of esophagus, gastroenterostomy in 2	0	0	3	Well, 5 to 14 mos
Reinhoff, 1951	Cirrhosis	6	2, ligation hep & splenic arteries. 4, ligation hep arteries	0	0	6	Well to 3½ yrs
Leger et al, 1951	Cirrhosis	1	Ligation hep art	0	0	1	No follow-up note

Julian and Fildes, 1951	Portal thrombosis	1	Esophagogastrectomy	0	0	1	Well, time not stated
Julian and Fildes, 1951	Cirrhosis	1	Ligation splenic vein	1	100		
Gerbode and Holman, 1951	Cirrhosis	1	Ligation splenic artery Omentopexy	0	0	1	Well 11 mos except for some edema
Gerbode and Holman, 1951	Extrahepatic thrombosis	2	1 Ligation gastric & splenic veins & splenic artery, omentopexy 1 Division gastric, esophageal, & duodenal veins Omentopexy	0	0	2	Well 2½ to 4 yrs
Linton, 1951	Cirrhosis	2	Portacaval	0	0	2	Failure of splenorenal
Linton, 1951	Cirrhosis	1	Sup mesenteric to vena cava	1	100	0	
Thorek, 1951	Portal hypertension	5	Ligation hep art	1	20	4	4 improved Time not stated
Phemister, 1951	Banti's disease	2	Gastrectomy, 1 partial, 1 total	0	0	2	1 bled for 3 yrs, well at 3½ yrs 1 well, time not stated, but had a baby
Berman et al., 1951	Cirrhosis	1	Ligation hep & splenic arteries	0	0	1	Well, time not stated

TABLE 13

OTHER OPERATIONS ON EXTRAHEPATIC CIRCULATION (*Continued*)

AUTHOR AND DATE	PRIMARY DISEASE	NUMBER OF CASES	OPERATION	MORTALITY		SURVIVORS	FOLLOW-UP
				Number	Per cent		
Jennings, 1952	Cirrhosis	3	Ligation hep & splenic arteries	1	33 3	2	1, 2 paracenteses in 1½ mo, well 3 mos 1, well 10 mos
Jackson, 1952	Not cirrhosis	1	Ligation hep & splenic arteries	0	0	1	Well, time not stated
Chenoweth, 1952	Cirrhosis	2	Ligation hep art	0	0	2	Well 3 to 11 mos
Large et al, 1952	Polycythemia & portal thrombosis	1	Omentorenal shunt	0	0	1	Well 11 mos
Large et al, 1952	Extrahepatic thrombosis	1	Sup. mesenteric to vena cava	0	0	1	Well 25 mos
Large et al, 1952	Cirrhosis	1	Umbilical vein to vena cava	0	0	1	Well 23 mos
Berman and Hull, 1952	Cirrhosis	12	Ligation hep, left gastric, & splenic arteries (Minor variations)	3	25	9	2 deaths 2½ & 5 mos. post-op 7 well, time not stated.
Altmeier, 1952	Cirrhosis	7	Ligation hep & splenic arteries	1	17.3	6	2 follow-up bleeding. 1 continued liver deterioration 3 fairly well, time not stated

Rousselot, 1952	Extrahepatic thrombosis	1	Sup mesenteric to vena cava	0	0	1	Well to 6½ mos
Blakemore 1952	Cirrhosis	4	"other"	3	75	1	Well, time not stated
Blakemore, 1952	Extrahepatic thrombosis	12	"other"	2	16 6	10	Well, time not stated
Walker, 1952	Cirrhosis and extrahepatic thrombosis	1	Esophageal transection	0	0	1	Well, time not stated
Walker, 1952	Extrahepatic thrombosis	1	Rt ovarian to portal vein as 1st stage Esophageal resection 2nd stage	0	0	1	Well, time not stated
Crile, 1952	Extrahepatic thrombosis	7	Transesophageal ligation of esophageal varices	0	0	7	2 postop bleeding, 5 well 1 to 18 mos Varices disappeared in 6
Blakemore, 1952	Extrahepatic thrombosis	4	"other"	3	75	1	Well, time not stated
De Britto, 1952	Extrahepatic thrombosis	1	Reno-gastro-epiploic shunt	0	0	1	Well, time not stated
Child, 1953	Extrahepatic thrombosis	1	Esophagogastrectomy	0	0	1	Bled following splenorenal shunt
Child, 1953	Extrahepatic thrombosis	1	Portacaval shunt Sup mesenteric vein graft	0	0	1	Closure of splenorenal shunt

shunts. There were 4 postoperative deaths, one on the day of operation due to extensive bleeding from the entire operative field including the site of the anastomosis, and one at eleven days due to liver failure and low salt syndrome with a thrombosed shunt. A third patient died on the twenty-first postoperative day of liver failure associated with agonal bleeding. The shunt in this case was also patent #26–R S died of liver failure five days postoperatively This patient was one of the poorest operative risks and was subjected to the operation with the balloon in place as a last effort to control bleeding

In three other patients in this series, it was necessary to continue the balloon tamponade throughout the operation. All three (#5, #7, and #25) did well and left the hospital improved by their operative procedure Even today, most surgeons interested in portal hypertension hesitate to recommend portal decompression as an emergent procedure Yet, in these three patients the shunt, performed on all but an emergency basis, proved to be life-saving As pointed out elsewhere, Blakemore, and Linton and Warren and others have sought to avoid performing portacaval shunts as emergency operations by direct surgical control of the hemorrhage. This has been accomplished transthoracically by suture ligature of the bleeding varix or varices

Although too early to generalize on the ultimate place of portal decompression in the treatment of portal hypertension, it seems reasonable to say that bleeding can be effectively controlled when it is possible to construct an adequate anastomosis. In unselected cases, sodium and water retention appears to be aggravated rather than improved as a result of portal decompression It also appears

*Non-Shunting Procedures for the Relief of Hemorrhage from Esophagogastric Varices**

Not infrequently patients are encountered in whom it proves impossible for one reason or another to construct a satisfactory venovenous shunt When such patients continue to bleed, every incentive appears to attempt some other form of operation to prevent further hemorrhage The most important of these substitute procedures is *esophagogastrectomy* This operation was devised by

* A reasonably complete list of surgical procedures, other than portacaval or splenorenal shunts, which have been performed, for one reason or another, upon the extrahepatic circulation is given in Table 13

Phemister and Humphreys in 1947 Encouraged by their success in treating esophagogastric cancer by this means, they proposed the operation as a life-saving measure for patients with bleeding from esophageal varices (Wangensteen, in discussing Phemister's original report, added another concept, namely, that acid-peptic erosion of the esophagus was the actual cause of bleeding from the

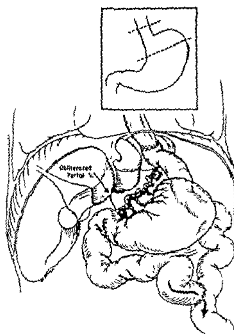


Fig 78 In this young woman with an extrahepatic block and a thrombosed splenorenal shunt, esophagogastric hemorrhage was finally controlled successfully by esophagogastrectomy, a Finney pyloroplasty, and a Roux in Y esophagojejunostomy (See portal venogram, Fig 83) (From Child and Payne Portal Hypertension Monographs in Medicine Williams & Wilkins Co)

varices, and advocated in addition to resection of the portion of the esophagus bearing the varices, a total resection of the stomach This approach to the treatment of bleeding varices was widely elaborated by Baronofsky, and together he and Wangensteen proposed total gastrectomy as an operation directed neither toward lowering portal pressure nor removing the site of hemorrhage Their obvious objective was to prevent acid-peptic regurgitation into the esophagus.

Several other prominent American surgeons have been attracted to esophagogastrectomy, and recently Womack and Gray and Whitesell have advocated a local resection combined with splenectomy. The latter authors have also added vagotomy in order to eliminate the cephalic phase of acid gastric secretion. Yet another type of operation which has been successfully applied to the solution of this problem is a limited esophagogastric resection followed by reconstruction of the enteric canal by means of a Roux in Y esopha-



Fig 79 D.R N.Y.H #576,553. *A* Esophageal varices prior to partial esophagogastrectomy with a Roux in Y esophagojejunostomy *B* Esophagogram two months after a partial esophagogastrectomy with a Roux in Y esophagojejunostomy This patient has not bled in over eighteen months since this operation was performed

gojejunostomy. This procedure is shown in Figure 78 Interestingly

[illegible]

and B)

In addition to resection of various types, other procedures have been suggested and tried to a limited degree Som and Garlock reported two patients in 1947 in whom they had *packed the upper thoracic mediastinum with gauze in the hope that the granulations forming in response to this foreign material would lead to the development of a periesophageal venous plexus capable of reducing the pressure in the submucosal esophageal varices.* Recently these two authors reviewed their results with this method of treatment in 8 patients. They still express the belief that this technique may have

some merit. Few others, however, have accepted their suggestion. *In one case so treated in* The New York Hospital, *attacks of esophageal hemorrhage continued unaltered.*

Many years ago, Blain advocated *ligation of the splenic artery* in patients with bleeding varices on the basis that this vessel contributes importantly to the total amount of blood entering the portal system. Holman in 1933, and recently Blain and Blain have again advocated *splenic arterial ligation. No very real measure of success has been achieved by this procedure alone. Of course, it differs* importantly from splenectomy alone, for in it the spleen and the associated communications which have been built up between the portal and systemic circulations are preserved.

Currently, the most controversial aspect of the treatment of varices concerns *hepatic arterial ligation.* The experimental basis for this procedure as well as some of the animal work has been reviewed in an earlier section. As far as man is concerned, ligation of the hepatic artery as a treatment for bleeding esophageal varices due to cirrhosis was first suggested by Rienhoff in 1951. Aside from theoretical considerations, the strongest stimulus to try this procedure in man has been the fact that portal decompression is a long and hazardous operation which will, it appears, always be limited in application. Hepatic arterial ligation, if it proves effective, is, in comparison to a venovenous shunt, a relatively simple surgical procedure which would not overtax the skill of the general surgeon who has not had special training in vascular surgery. Shortly after its introduction by Rienhoff, the operation was taken up enthusiastically by Berman and others.

At the moment Rienhoff reports that of the 21 cases he has operated upon, 14 are alive and markedly improved. Of the 7 who died, 4 were bleeders. They were almost moribund on admission and expired within fourteen days after operation. The remaining 3 died of recurrent hemorrhage from three to six months after operation. In discussing his operation, namely, ligation of the common hepatic, splenic, and gastric vessels, Rienhoff emphasizes his conviction that even in the normal liver, the common hepatic artery can be ligated without gross hepatic infarction. In commenting upon the patients who were improved, Rienhoff records that 9 had severe ascites from which they have received complete relief. In these patients, the hepatic artery was tied distal to the duodenal, and the splenic was also ligated. Four patients with both ascites and hemorrhage have been relieved of their ascites, but two have continued to bleed. In conclusion, Rienhoff states that at the moment he feels hepatic, splenic, and gastric arterial ligation is the procedure of choice for the patient with ascites, the portacaval shunt may be the better

operation for bleeding esophageal varices, although this has not been proved

In Dr Rienhoff's letter to me he requested that I quote him as saying that, "More cases must be done and further studies made on

any dogmatic state-

, he also stated that, "Unless one ligates the hepatic artery distal and proximal to the gastroduodenal, one will get a collateral circulation . . . which will nullify any benefits of ligation"

In addition to Rienhoff's experiences Berman reports that to

es) the left

classified as postoperative deaths Seven died within a year Of these 13 deaths, 6 were from hemorrhage from esophageal varices and 3 from recurrent ascites and hepatic insufficiency. The average survival time has been eleven months The longest survival time was recorded in one patient who is reported to be well and back at work twenty-six months after operation At the present time, Berman lists active hemorrhage, persistent jaundice, hypertension, cardiac decompensation, and an extremely large liver which is rapidly shrinking in size as contraindications to hepatic arterial ligation. Hepatic necrosis has not been a complication, for in every instance the hepatic artery has been ligated on the aortic side of the gastroduodenal artery Of the 26 patients, 13 or 50 per cent are alive without ascites or bleeding. Berman's final word in a letter of recent date emphasizes two points, first that he is trying to restrict the operation to patients with atrophic cirrhosis, and second, that he considers the operation in the early experimental stage An elaborate presentation of Berman's main points together with a complete discussion of these can be found in a paper read before the Western Surgical Association and published in Archives of Surgery in July, 1952.

In a recent conversation, Madden, who has ligated the hepatic artery of 8 patients, expressed great doubt as to the efficacy of the procedure, for in none of his patients could he detect significant improvement

At the present time, it is difficult to evaluate this newest surgical procedure directed toward the relief of portal hypertension and ascites. Some reports are enthusiastic, others discouraging. The method is generally being applied today to patients who are considered too poor risks to tolerate a more extensive operation In light of the evidence available to date, it seems justifiable to conclude that

the method of the selection of patients is at fault Perhaps as time goes on those who can be expected to benefit may be selected with greater accuracy The exponents of hepatic arterial ligation make one point which hypothetically is in their favor They believe that *hepatic arterial ligation at least implies an effort toward improving* liver function Those who advocate portacaval shunts would be hard put to it to make a similar claim

The Selection for Operation of Patients with Portal Hypertension

[illegible]

site of hemorrhage In general, these are young individuals with good hepatic reserve who could be expected to tolerate any operative procedure well In the majority of instances, they can be expected to survive splenectomy and a splenorenal shunt Occasionally, a vein graft will facilitate the procedure The unhappiest consequence of this operation is associated with closure of the splenorenal shunt and recurrent hemorrhage Should this occur, a second attempt should be made at decompression If this, too, is unsuccessful or impossible, some form of esophagogastric resection would appear to be indicated To date, hepatic arterial ligation has not been recommended

Patients with intrahepatic block due to cirrhosis, however, present quite a different problem They all require careful study and evaluation before portal decompression is recommended In certain instances, the decision will not be difficult In those patients whose hepatic reserve is excellent and who have recovered promptly after their hemorrhage, operation can be recommended enthusiastically as an important life-saving procedure The operation should be denied to patients to whom Blakemore is wont to refer as "dead end cirrhotics" Their recovery after hemorrhage is slow, they are persistently jaundiced, and the disease in them is usually associated with ascites Such patients may be suspected of being upon the verge of hepatic failure, and unless they respond dramatically to medical therapy, they should probably be refused an attempt at portal decompression Between these two extremes lies a group of patients in whom the risk of death due to hepatic failure must be [illegible]

Linton has made a most constructive effort to define those patients with cirrhosis who are suitable candidates for operation With a

few modifications, Linton's classification is outlined in the following paragraphs

CIRRHOSIS HEMORRHAGE WITHOUT ASCITES OR JAUNDICE. In general, any patient with cirrhosis who has had a massive esophagogastric hemorrhage must be considered a candidate for surgical intervention At the present time, the most useful operation is portal decompression by means of either a portacaval or splenorenal shunt. Whether other less formidable surgical procedures will be developed in the future is difficult to forecast At the moment, portal decompression appears to be the operation of choice. Since this is a surgical operation of some magnitude, the patients in whom it is to be used must be evaluated with care in terms of the surgical risk involved

decompression. The absence of ascites or jaundice means that hepatic reserve is good and that in all probability the patient will withstand the procedure well Lichtman has pointed out in this connection that hematemesis often immediately precedes jaundice and ascites Blakemore, on the other hand, has expressed in his many writings the opinion that hemorrhage is a catastrophe tolerated but poorly by the patient whose liver is near the brink of decompensation.

CIRRHOSIS HEMORRHAGE WITH ASCITES AND/OR JAUNDICE Once a patient with cirrhosis has decompensated as judged either by the appearance of ascites or jaundice or both and then has a severe esophagogastric hemorrhage, the decision whether to subject him to portal decompression is difficult indeed Once either of these two signs appears, the prognosis as to life is poor, irrespective of

a year of their first hemorrhage It is in this group of patients that the surgical mortality is high After operation, such patients may pass into hepatic coma and anuria, they may become deeply jaundiced and may secrete excessive amounts of ascitic fluid Probably the best hope for such patients lies in a carefully regulated and oftentimes prolonged period of preoperative preparation. If by the judicious use of diuretics, low salt diets, and the administration of plasma, blood, and serum albumin, the patient can be brought into reasonable balance, he may withstand the operation surprisingly well. The decision as to whether portal decompression is advisable in this group must rest with the individual patient's response to a sound medical program.

Under this same heading will also be found a group of patients whose hemorrhage has precipitated an attack of ascites and deepening jaundice Instead of stopping, the hemorrhage continues and can perhaps only be held in check by balloon tamponage. What to suggest for these patients is difficult indeed, for the balloon cannot be left in place safely for more than a few days, and generally they are in such poor condition that an emergency portacaval shunt is out of the question It is in these patients that Boerema, Crile, Blakemore, and Linton have attempted transthoracic and transesophageal ligation of the bleeding varices as a temporary measure designed to tide the patient over his immediate crisis If, with the hemorrhage controlled, a proper medical program leads to remission of signs and symptoms, operation may be undertaken If, however, hepatic decompensation continues, it seems unlikely that the patient will survive the surgical procedure Operation should be withheld under these circumstances, for there is little point in needlessly adding to the mortality

CIRRHOSIS WITHOUT HEMORRHAGE OR VARICES Patients in whom a diagnosis of varices cannot be made with relative ease and who have never bled should, in the light of present knowledge, not be operated upon Portal decompression does not, as far as is known, improve hepatic function nor does it increase the reserve of this organ. There seems, therefore, little reason to decompress the portal bed in patients with uncomplicated cirrhosis

CIRRHOSIS WITHOUT HEMORRHAGE BUT WITH VARICES With increasing awareness of portal hypertension, many patients today are subjected to roentgen esophagography or to esophagoscopy in search of varices In many clinics, this effort has been rewarded by the demonstration of dilated esophageal veins which may be interpreted as positive evidence of portal hypertension Today, there is little unanimity of opinion as to whether operation is advisable in such individuals Julian and Fildes have expressed the belief that operation should be resorted to when varices are demonstrated provided there is reasonable hepatic reserve Linton opposes this view Blakemore, at a recent meeting, suggested that as more evidence accumulates it may prove important to operate upon these individuals, for even a simple hemorrhage may throw a patient with cirrhosis into hepatic decompensation from which he does not commonly recover If at all possible, even one hemorrhage is to be avoided At The New York Hospital, a dozen or more individuals falling into this category are now under close surveillance If over a period of time the incidence of hemorrhage can be shown to be high in these patients, the present policy of not operating upon them will doubtless be changed A most interesting commentary upon this is found in a recent paper

by Dye and his associates who followed 11 patients with known portal hypertension They were able to demonstrate that the increased portal pressure fluctuated from time to time. Under medical management, it might entirely regress Rather justly, these authors point out that disappearance of esophageal varices is not necessarily evidence of a successful portacaval shunt. This may occur quite independently of whether the shunt functions or not and probably is related to changes within the liver itself. The findings of this careful study should be corroborated by additional cases before they are widely accepted If these observations be true, one of the most useful yardsticks for measuring the effectiveness of portal decompression loses much of its value.

CIRRHOSIS WITH UNCONTROLLED ASCITES In line with Eck's original suggestion, many have been persuaded that a successful portacaval shunt would prove useful in controlling ascites. As soon as the technique for performing such a shunt successfully was developed, many patients with ascites were operated upon with this as the primary indication The results have been uniformly disappointing Not only was the ascites unaffected, but the postoperative mortality proved prohibitively high

Liver Function Tests as an Aid in Selecting Patients for Portal Decompression

While significant advances have been made in estimating liver function by means of biochemical tests, attempts to select patients for portal decompression on the basis of a fixed pattern of such tests have been disappointing However, in the evaluation of any individual patient's problem, certain information derived from these procedures is invaluable In general, the levels of serum albumin and serum bilirubin seem most closely correlated with the observed clinical course. Patients with albumin levels of 3 grams per 100 ml or below tolerate operation poorly and usually develop persistent postoperative fluid retention. Likewise, operation is not advised if the serum bilirubin rises much above 4 mg. per 100 ml. Patients with high serum bilirubin levels have been frequently observed to develop cholemia following the long operative procedure and to present major problems in management. Significantly prolonged prothrombin times which are not correctable by vitamin K also render operation hazardous due to uncontrollable bleeding. Other clinics have found a correlation between high Bromsulphalein retention and postoperative morbidity This test is an indication of parenchymal cellular function and as such is a valuable screening procedure.

operation is of necessity dictated by the course of the patient.

CHAPTER 14

Portal Venography

WITH the development many years ago of several radio-opaque substances which could be injected safely into various of the body's vascular systems, angiography became an accepted diagnostic technique Cerebral angiography, angiocardiography, peripheral angiography, phlebography, and aortography are today important aids in the diagnosis of obscure vascular anomalies and diseases. The application of these techniques to the portal venous system has been slow, primarily because of the difficulties encountered in attempting roentgenography in operating rooms where explosive gases are commonly employed Direct portal venography requires that the patient be in an operating room and under a general anesthesia, for only by cannulating one of the branches of the portal vein can a contrast medium be injected with sufficient rapidity to produce useful diagnostic films Until an x-ray apparatus with rapid cassette changers is manufactured which can be used safely in the presence of explosive gas mixtures, portal venography will lag behind in its development

[illegible]

with an extraordinarily useful research tool. In Figure 80 are reproduced a series of Daniel's roentgenograms of the hepatic portal venous circulation When serial films such as these become available for the study of the portal system in man, this section on venography will have to be entirely rewritten

Interest in portal venography was aroused in the surgical research laboratories of The New York Hospital through our studies upon portal hemodynamics in the Macaca mulatta monkey. Having proved that this animal survived sudden portal occlusion, my associates and I became interested in following portal blood flow during the immediate and late postoperative course After studying a num-

[illegible]

and could not be traced or mass injections, because of poor pressure

control, gave entirely false results We then began to study the obstructed portal system in the living dog by means of roentgen visualization of the splanchnic bed after it was injected with 35 per cent or 70 per cent Diodrast The results with this technique were most gratifying, and since its adoption a few years ago over one hundred portal venograms have been performed in monkeys and in dogs Our latest application of this method has been in connection with our studies upon portacaval transposition and hepatic regeneration A number of these research venograms are reproduced in the appropri-

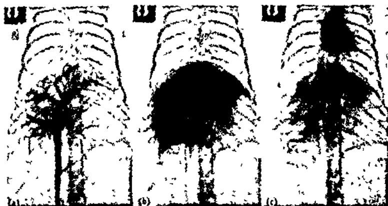


Fig 80 One of Daniel and Prichard's serial hepatograms Application of this technique to man is an ideal as yet unrealized (a) Portal venous filling (b) Sinusoidal filling (c) Hepatic venous filling (From J Path & Bact, vol 64, 1952)

ate appendices Here, however, attention will be focused upon visualization of the portal vein in various diseases of man Because no great number of these films are available for study, a complete diagnostic survey is impossible In the next few pages is reproduced a random series of portal venograms illustrative more of the potential value of the method than of its actual accomplishments As time goes on and improved techniques become available, it seems safe to predict that this field of angiography will be greatly expanded Among others interested in this field at the present time are Moore and Bridenbaugh Rousselot, Leger and Santy and Manon

Technique

Early in our experience with portal venography a 15 bore needle was inserted into the superior mesenteric vein or one of its large tributaries as this large vessel disappeared from view beneath the

CHAPTER 14

Portal Venography

WITH the development many years ago of several radio-opaque substances which could be injected safely into various of the body's vascular systems, [illegible] nique Cerebral a[illegible] graphy, phlebogr[illegible], and aortography are today important aids in the diagnosis of obscure vascular anomalies and diseases The application of these techniques to the portal venous system has been slow, primarily because of the difficulties encountered in attempting roentgenography in operating rooms where explosive gases are commonly employed. Direct portal venography requires that the patient be in an operating room and under a general anesthesia, for only by cannulating one of the branches of the portal vein can a contrast medium be injected with sufficient rapidity to produce useful diagnostic films Until an x-ray apparatus with rapid cassette changers is manufactured which can be used safely in the presence of explosive gas mixtures, portal venography will lag behind in its development.

The usefulness of portal venography and hepatography is not limited to general surgical operating rooms. Its development in the past few years by Daniel and his associates has provided physiology with an extraordinarily useful research tool In Figure 80 are reproduced a series of Daniel's roentgenograms of the hepatic portal venous circulation. When serial films such as these become available for the study of the portal system in man, this section on venography will have to be entirely rewritten.

Interest in portal venography was aroused in the surgical research laboratories of The New York Hospital through our studies upon portal hemodynamics in the Macaca mulatta monkey. Having proved that this animal survived sudden portal occlusion, my associates and I became interested in following portal blood flow during the immediate and late postoperative course After studying a number of these animals at the autopsy table, it became obvious that little was to be learned at autopsy, either by simple observation or by mass injection techniques. All too often the veins were collapsed and could not be traced or mass injections, because of poor pressure

was planned, a short segment of the upper jejunum was drawn up into the wound, and a convenient mesenteric vein which approximated the diameter of the polyethylene catheter was selected After freeing this vessel of adjacent fat and peritoneum, it was incised between occlusive tension sutures and the catheter inserted into it for a distance of about 3 to 4 cm Here it was tied in place and the outer end attached to a #15 needle The 6 cm of catheter outside the vein then provided adequate slack with which to absorb the inadvertent movements of the patient and operator At first 35 per cent Diodrast was used, but as we became bolder 70 per cent solutions were used in 40 to 50 ml amounts Some sixty venograms have [illegible] his [illegible] of [illegible]



Fig 82 This portal venogram was obtained in patient E C, N Y H #584,-105, during the course of exploration for chronic, recurrent pancreatitis It is considered normal The crescentic shadow at the tip of the needle in the lower right hand corner of the film is due to the stream of splenic venous blood entering at this point The blob of radio-opaque substance in the lower center is in the gallbladder A cholangiogram had been performed just prior to the venogram

inferior border of the head of the pancreas. At best, this was a harrowing performance because motion on the part of the operator or of the patient often dislodged the needle from the lumen of the vein All too often, a large portion of the Diodrast was delivered freely into the peritoneal cavity or, should the needle have penetrated

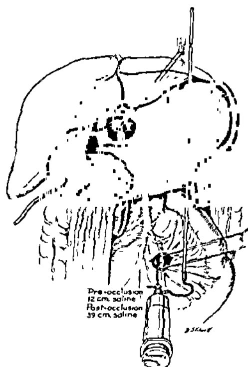


Fig 81. Technique of portal venography and manometry. Originally the contrast medium was injected
found to be too harrowing for [illegible]
vein or penetrated the vessels' f[illegible]
polyethylene catheter tied in place improved the quality of the venograms immeasurably

the far side of the vessel, into the retroperitoneal tissues To add to

[illegible]

paper in 1950 we changed our technique and used a short length of a polyethylene catheter instead of the needle Immediately upon opening the peritoneal cavity of a patient in whom portal venography



Fig 85 Legend below

Fig 83 D R N Y H #576,553 This venogram depicts accurately the status of the portal circulation of a patient with severe extrahepatic block The dye enters the portal system through the fine catheter visible in the left lower quarter of the illustration Here it is dissipated in a cavernomatous mass of veins, on the far side of which it is picked up and returned to the general venous system through the inferior mesenteric vein (lower right) and through the coronary system (upper mid section) The varices in the stomach and lower esophagus are visualized

Fig 84 P R N Y H #598,106 Another example of extrahepatic block showing esophagogastric varices, inferior mesenteric collateral, and enormous varix formation in the hepatoduodenal ligament

Fig 85 Portal venogram obtained in patient E L, N E C H #75-431, whose extrahepatic portal block was presumably due to damage of the portal vein in the course of a cholecystectomy performed one year prior to death (see page 378 for complete case history) In this film the portal vein cannot be visualized nor can the splenic At the operating table it was postulated, therefore that neither a portacaval nor splenorenal shunt was indicated. At post mortem examination an extensive thrombosis with minor canalization of the portal and splenic veins was demonstrated



Fig. 83 See facing page for legend



Fig 84 See facing page for legend

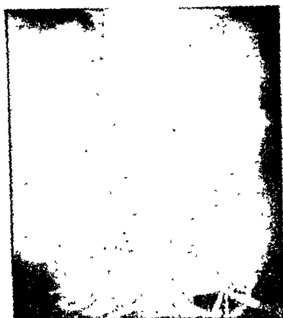


Fig 88 See below

Fig 86 G M N E C H #74-496 This patient's film is of interest, first, as an example of a perfectly normal portal venogram and secondly for the enormous size of the liver as reflected in the hepatogram This patient had had infectious hepatitis many years before and presented himself for hypersplenism needing splenectomy His portal pressure was 28 cm of saline This film proved particularly valuable, for it demonstrates a portal vein useful for shunting purposes should his portal hypertension ever become associated with varices and massive hemorrhage

Fig 87 R K N Y H #596,344 A portal venogram in a patient with cirrhosis portal hypertension, and esophagogastric hemorrhage Portal pressure was 34 cm of saline This demonstrates beautifully a large hypertensive portal vein eminently suitable for a portacaval shunt (Portacaval Case #8, p 359)

Fig 88 W K N Y H #431,204 This patient's venogram reveals an advanced intrahepatic block due to cirrhosis His portal pressure was 35 cm of saline This contrasts sharply with most of the films obtained in patients with cirrhosis in that the collateral pattern resembles that of an extrahepatic block Little if any of the radio-opaque material passes through the liver (Portacaval case #21, p 367)



Fig 86 See facing page for legend.



Fig 87. See facing page for legend.



Fig 91 See below.

Fig. 89 D K N Y H #582,973 Biliary cirrhosis of the liver The most [illegible]

Fig 90 M P N E C H #67-488 Portal venogram This patient had severe portal hypertension (49 cm of saline) due to cirrhosis The feature in this film is the two small areas of radiolucency visualized in the portal vein In the course of performing the portacaval shunt, these shadows were proved to reflect two areas of organized thrombus clinging to a sclerotic plaque in the wall of the vessel These were simply scraped off and a satisfactory shunt completed (Portacaval case #29, p. 371)

Fig 91 O.A. K H #44-899. Although this venogram is poor, it is reproduced for two reasons. First, it is the only one obtained in a patient with a severe intrahepatic block due to Schistosoma mansoni Second it shows the radio-opaque substance backing up into the splenic vein, filling the dilated and varicose coronary vein and also filling a huge duodenal vein (Portacaval case #22, p 367)



Fig 89 See facing page for legend.



Fig. 90. See facing page for legend



Fig 94 See below

Fig 92 A K N Y H. #498,896 This imperfect venogram reveals a widely patent portacaval shunt approximately three months after its construction Of particular interest in this patient were her portal pressures Preshunt—46 cm of saline, immediate postshunt—23 cm of saline, three months postshunt —11 cm of saline (Portacaval case #16, p 363)

Fig 93 S L N Y H #569,381 This portal venogram was obtained in a patient with portal hypertension The portal vein is enlarged, and the liver fills well Although there was sufficient intrahepatic block to cause varices which bled there is a generous amount of dye entering the liver This is in sharp contrast to the film reproduced in Figure 88 in which the degree of intrahepatic block is sufficient to divert practically all of the Diodrast into the coronary and inferior mesenteric veins (Portacaval case #6, p 358) (From Child et al Radiology, vol 57, 1951,)

Fig 94. M F N Y H #622,597 This film is an example of a large, extrinsic pressure defect due to a carcinoma in the head of the pancreas Portal pressure was 20 cm of saline Because of hepatic metastases, this tumor was inoperable



Fig 92 See facing page for legend



Fig 93. See facing page for legend



Fig 97 See below

Fig 95 R McN N Y H #632,433 This patient was admitted to the hospital deeply jaundiced Deep in the hilum of the liver could be palpated a stony, hard mass, biopsy of which revealed carcinoma The common duct was collapsed and without bile This venogram shows a sharply constricted area in the portal vein in its intrahepatic portion It lies just at the point of division of the portal vein into the right and left branches

Fig 96 J M N Y H #578,518 This portal venogram shows complete or practically complete obstruction of the superior mesenteric vein by a carcinoma primary in the uncinate process of the pancreas Large and small collaterals developing intestinalwards to the obstruction are nicely seen The portal pressure was 27 cm of saline (From Child et al Radiology, vol 57, 1951)

Fig 97 Portal venogram obtained in a patient with advanced cirrhosis of the liver and a high portal pressure. The unusual crescentic defect was due to a greatly hypertrophied caudate lobe (Courtesy of Dr John Beal)



Fig 95 See facing page for legend



Fig. 96. See facing page for legend



Fig 100 See below

Fig 98 D McC N Y H #604,762 Severe angulation of the portal vein due to a carcinoma primary in the body of the pancreas

Fig 99 S S N Y H #564,393 Carcinoma of the gallbladder Hepatic metastases This film reveals a large tumor mass (T) in the right upper quadrant and an enormous hepatic metastasis (M)

Fig 100 F S N Y H #192,002 This venogram reflects accurately complete obstruction of the portal vein by a carcinoma (inoperable) of the head of the pancreas In most other occlusions of the portal vein the inferior mesenteric bears the brunt of the collateral flow Here it is the right colic vessels (From Child et al Radiology, vol 57, 1951)



Fig. 98 See facing page for legend.

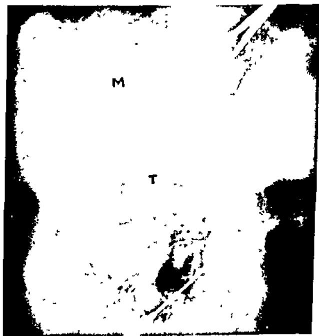


Fig 99. See facing page for legend.

CHAPTER 15

Pancreaticoduodenectomy with Resection of the Portal Vein

IN 1938 Whipple and his associates announced that they had successfully resected the head of the pancreas and the duodenum for a malignant pancreaticoduodenal tumor Within a few years, a number of surgeons over the country reported that they, too, had successfully performed Whipple's operation Great hope then was expressed that tumors primary in or about the head of the pancreas had at last been brought within reach of surgical therapy During the past few years, about 150 of these resections have been reported with sufficiently long follow-up studies to permit a preliminary evaluation of the results In Table 14 are summarized the most recent reports available Of the hundred odd recorded cases of primary pancreatic cancer, the average survival time has been fifteen months, and only about three patients have been reported alive over five years These manifestly poor results have prompted a number of vigorous reactions, some surgeons have expressed the opinion that the salvage from the Whipple operation was no better than that obtained by palliative decompression of malignant obstruction of the biliary tract Others have felt that the operation should be abandoned, either entirely or at least until such time as patients with pancreatic cancer can be brought to operation earlier Still others believe that such a pessimistic approach is inconsistent with progress in surgery

As this operation is usually performed today, it is technically imperfect Although generally designated as a radical procedure, this is far from the actuality Despite the fact that a generous segment of stomach, the entire duodenum, and upper jejunum, the lower common duct and as much as the entire pancreas is often removed,

[illegible]
nant process, the operation has been abandoned For this reason, the



Fig 101 G K N Y.H. #636,202 Inoperable cancer of the head of the pancreas This film demonstrates marked distortion and narrowing of the portal vein without complete obstruction Here collaterals appear to be composed primarily of retropancreatic anastomoses

CHAPTER 15

Pancreaticoduodenectomy with Resection of the Portal Vein

IN 1938 Whipple and his associates announced that they had successfully resected the head of the pancreas and the duodenum for a malignant pancreaticoduodenal tumor Within a few years, a number of surgeons over the country reported that they, too, had *successfully performed Whipple's operation* Great hope then was expressed that tumors primary in or about the head of the pancreas had at last been brought within reach of surgical therapy During the past few years, about 150 of these resections have been reported with sufficiently long follow-up studies to permit a preliminary evaluation of the results In Table 14 are summarized the most recent reports available Of the hundred odd recorded cases of primary pancreatic cancer, the average survival time has been fifteen months, and only about three patients have been reported alive over five years These manifestly poor results have prompted a number of vigorous reactions, some surgeons have expressed the opinion that the salvage from the Whipple operation was no better than that obtained by palliative decompression of malignant obstruction of the biliary tract *Others have felt that the operation should* be abandoned, either entirely or at least until such time as patients with pancreatic cancer can be brought to operation earlier Still others believe that such a pessimistic approach is inconsistent with progress in surgery

As this operation is usually performed today, it is technically imperfect Although generally designated as a radical procedure, this is far from the actuality Despite the fact that a generous segment of stomach, the entire duodenum, and upper jejunum, the lower common duct, and as much as the entire pancreas is often removed, the portal vein is routinely left in place This structure, often lying within millimeters of the neoplasm, either has been left with tumor invading its wall or because of its obvious involvement in the malignant process, the operation has been abandoned For this reason, the

TABLE 14

RADICAL PANCREATICODUODENECTOMY FOR CANCER OF THE PANCREAS

a Summary of Radical Pancreas Operations (27)

HOSPITAL	PAN-CREAS NO	PAPILLA NO.	COMMON DUCT NO	DUO-DENUM NO	ISLET CELL NO	TOTAL PANCREATEC-TOMY NO	BENIGN LESIONS NO
Columbia-Presbyterian	18	22	9	7	2	7	8
10 46-10 50 24—2-8.3% mortality							
Lahey Clinic	42	26	4	7			11
In last 41 cases, 3 deaths-7.3%							
Mayo Clinic	27	17		3	1	1	
Memorial Hospital	34	2	1	7		4	
NYH-Cornell	13	6		4		1	
Total 5 year survivors	134 3						

Total postoperative deaths 65
Total mortality 24%

b. Radical Pancreaticoduodenectomy for Primary Pancreatic Cancer Postoperative Mortality and Survival Period Collected Cases

AUTHOR	NO CASES	NO P O DEATHS	NO SURVIVORS				
			Total	Dead 1 9 mos	Dead 10-14 mos.	Alive at time of report	Alive over 18 mos.
Fallis and Szilagyi	3		3		2	1 at 3 mos	
Dennis	8	2	4			1 at 6 mos 1 at 12 mos.	
Cole and Reynolds	4	1	3			1 at 4 mos. 1 at 7 mos 1 at 14 mos	
Miller et al	27	8	19	Average survival of 13 cases was 12 mos.		1 at 15 mos. 1 at 11 mos.	4
Cattell and Pyrtek	30	5	25	Average survival of 18 cases was 11 mos		1 at 15 mos 1 at 12 mos 3 less than 12 mos.	2
Bartlett	13			Average survival was 8 mos		1 at 8 mos.	1 (?)
Parsons	?	?	5	3			2
Brunschwig	2		2	1		1 at 15 mos	
Brunschwig	5	3	2	2			
Harvey and Oughterson	5	1	4	2		2 at 9 mos	
Orr	2		2	1		2 at 3 mos	

Total cases 49
Total P O deaths 20
P O mortality 20%
Total survivors 71
Average survival period of those reported dead 9 mos.
Total reported surviving over 18 mos 9

From Child, et al., Surg., Gynec. and Obst., 94:31-35, 1952

experiments which have been recorded elsewhere in this volume (Appendix 2) were started in an effort to determine whether or not this vessel could be resected were it invaded by cancer. To date, 4 patients have been subjected to a two-stage operation at which resection of the portal and superior mesenteric veins was combined with pancreaticoduodenectomy In one patient, a single-stage procedure was attempted without fashioning a shunt between the portal and systemic venous system This patient died in shock shortly after operation, bleeding during the procedure became uncontrollable as soon as the portal and superior mesenteric veins were resected In these two respects, this ill-fated, one-stage operation reproduced precisely the results obtained in the monkey where pancreatectomy with resection of the portal vein was attempted at a single sitting Because of their interest, these 4 case reports have been outlined in detail as follows

TWO STAGE RADICAL PANCREATICODUODENECTOMY WITH RESECTION OF THE PORTAL VEIN FOR METASTATIC MELANOMA

Case #1—M B—N.Y H #425,559—Age 47 Years Admitted April 17, 1951 Discharged June 2, 1951

HISTORY This forty-seven-year-old housewife of Russian extraction was first admitted to The New York Hospital in October of 1945 for pain in the left arm and hand The left anterior scalenus muscle was resected, and she was discharged improved Two years later, she was again admitted for recurrence of pain in her left arm, and at exploration a metastatic, malignant melanoma was excised from her brachial plexus on this side

She was admitted in 1951 because of jaundice of two weeks' duration The patient stated that she had been quite well until the onset of what she considered her present illness At that time, she developed epigastric distress after eating fatty or greasy foods This indigestion continued for the next two weeks Her appetite failed entirely, and she lost ten pounds in weight Two weeks before admission, her skin and sclerae became icteric, her urine dark, and her stools gray in color

Aside from the malignant melanoma removed from her axilla four years prior to her present admission and the events constituting her present illness, her history was negative

PHYSICAL EXAMINATION This woman was well nourished and, save for her obvious jaundice, appeared to be in good health General atrophy of all muscles of her left arm and hand was present Her abdomen was soft and flat A mass, believed to be liver, was palpable about 3 cm below the right costal margin This was smooth and non tender The spleen could not be felt, and pelvic and rectal examinations were negative

TABLE 15

PREOPERATIVE AND POSTOPERATIVE BLOOD STUDIES ON CASE 1

DATE	BL UREA N	SUGAR	MEq L.				PROTEIN GM 100 ML.				BILIRUBIN			ALK PHOS	THYM TURB	CEPH FLOC	CHOLESTEROL		PROTHROMBIN	
			CO₂ comb pwr	Chlorides NaCl	Na	K	Tot	S alb	S glob	Phos	Tot	Direct	Indir				Tot	Esters	Undil dil.	Control
Preoperative																				
4 18	9	89					7 9	4 9	3 0	4 5	9 6	6 3	3 3	11 0	4 0	5 0	238	130 7	14 7 33 6	14 0
4 19											12 6	7 2	5 4							
4 24							7 7	4 2	3 5	4 0	10 9	6 8	4 1	11 3			239 5	124 5		
4 29										4 4	9 4			15 6						
2										3 8	10 7			12 6					15 6 37 6	15 2 39 2
Postoperative st stage																				
4 PO 1			27	100	135	4 8				3 5	16 3	9 9	6 4	10 1	6 0	5 0				
7 PO 4	9				122	3 0	5 9	3 4	2 5	3 9	15 7	9 7	6 0	11 1	4 0	12 0				
8 PO 5			27	103	128	3 7					11 6									
9 PO 6							6 7	3 9	2 8	3 6	12 0	7 3	4 7	8 3	5 0	7 0			14 1	15 0

Postoperative 2nd stage																				
5 11 PO 8-1		143	29	96	135	5.2					11.0						275	147.6 53.7%		
5 12 PO 9-2	x		27	95	128	5.1														
5 14 PO 11-4	x		26	94																
5 15 PO 12-5			25		133	4.6	6.0	3.2	2.8	3.1	8.7	5.7	3.0	7.8						
5 16 PO 13-6			26	91	132	4.3	[illegible]	3.4	2.4	4.0	6.7					7.0				
5 17 PO 14-7			29	94	136	4.9	5.9	4.0	1.9	4.0				14.1						
6 18 PO 15-8			28	91	132	4.2	5.6	3.5	2.1	4.5	4.7			10.6						
5 19 PO 16-9			28	93	127	4.8														
5 21 PO 18-10	x		25	97	129	4.9	5.6	3.3	2.3	4.4	3.3			10.7	2.0					
5 28 PO 25-18											6.5	4.1	2.4							
5 29 PO 26-19										5.4	2.4			8.1						
5 31 PO 28-21		85					7.3	4.6	2.7	4.8	1.8			9.3						

From Child et al. Surg., Gynec. and Obst. 97:31-45, 1953.

TABLE 15

PREOPERATIVE AND POSTOPERATIVE BLOOD STUDIES ON CASE 1

DATE	BL UREA N	SUGAR	MEq /L				PROTEIN GM 100 ML				BILIRUBIN			ALK PHOS	THYM TURB	CEPH FLOC	CHOLESTEROL		PROTHROMBIN	
			CO_2 comb pwr	Chlorides NaCl	Na	K	Tot	S alb	S glob	Phos	Tot	Direct	Indir				Tot	Esters	Undil dil	Control
Preoperative																				
4 18	9	89					7 9	4 9	3 0	4 5	9 6	6 3	3 3	11 0	4 0	5 0	238	130 7	14 7 33 6	14 0
4 19											12 6	7 2	5 4							
4 24							7 7	4 2	3 5	4 0	10 9	6 8	4 1	11 3			239 5	124 5		
4 29										4 4	9 4			15 6						
5 2										3 8	10 7			12 6					15 6 37 6	15 2 39 2
Postoperative 1st stage																				
5 4 PO 1			27	100	135	4 8				3 5	16 3	9 9	6 4	10 1	6 0	5 0				
5 7 PO 4	9				122	3 0	5 9	3 4	2 5	3 9	15 7	9 7	6 0	11 1	4 0	12 0				
5 8 PO 5			27	103	128	3 7					11 6									
5 9 PO 6							6 7	3 9	2 8	3 6	12 0	7 3	4 7	8 3	5 0	7 0			14 1	15 0

dissected free at the porta hepatis and occluded for thirty min- [illegible] mm of mercury within ten minutes It then slowly returned to her normal level of 110/80 mm of mercury When her systemic blood pressure had stabilized at its normal level, the portal ve.n was doubly ligated, and the ends of the sutures left long for ready identification at the time of the next operation One hour after occlusion of [illegible] lessen while she was awaiting her next operation The wound was closed in layers with silk

FIRST STAGE POSTOPERATIVE COURSE This patient's course following ligation of her portal vein was uncomplicated Her temperature rose to 38 6 and 38 4 degrees centigrade during the evening of her second and third postoperative days By the fifth, she was taking a soft diet On the seventh, she was returned to the operating room for the second stage

Second Stage (May 10, 1951)—Radical Pancreaticoduodenectomy with Resection of the Portal Vein for Metastatic Malignant Melanoma, Pancreaticojejunostomy, Choledochojejunostomy, and Gastrojejunostomy

With the patient under intratracheal cyclopropane, the abdomen was again opened, this time through a generous upper abdominal curvilinear transverse incision Portal venography was repeated, and the film is reproduced in Figure 102 This was interpreted as revealing complete occlusion of the portal vein and extensive pelvic collaterals between the capillary beds of the pelvic and inferior mesenteric veins The portal pressure had fallen during the week to 23 cm of saline Because of the assurance of evidence derived from experimental work on the monkeys that it would be safe to operate through a field the venous pressure in which was only 23 cm of saline, it was decided to proceed with the resection of the tumor and the portal vein Prior to embarking upon the resection itself, the spleen was removed, for we believed that this would lower the portal pressure another 5 to 10 cm of saline

The resection proper was performed in the following steps The gallbladder was dissected free, its blood supply secured, and the common hepatic duct divided about 1 5 cm below the fusion of the right and left hepatic ducts The portal vein was divided between the previously placed ligatures The stomach was transected at the junction of its lower and middle thirds, and the pancreas at approximately the mid portion of its body Interestingly enough the splenic vein was divided just to the

LABORATORY DATA. A chest plate and bone series were negative for any evidence of metastases. A flat film of the abdomen was negative as was a barium enema. Gallbladder series were not performed because of her jaundice. Examination of the stomach and duodenum with barium led the roentgenologist to make a diagnosis of a neoplasm of the head of the pancreas which had invaded the distal stomach and the first, second, and third portions of the duodenum. Intravenous pyelography revealed normally functioning kidneys bilaterally. An ophthalmological consultant stated that her fundi were normal.

Her hemoglobin was 13.7 grams, red blood count—5.3 million, white blood count—13,100, 25 per cent leukocytes, 7 per cent monocytes, 68 per cent polymorphonuclear leukocytes. Routine urinalysis was negative. The urine was positive for urobilinogen and for melanin. The stools were greenish brown and consistently positive for blood.

For complete preoperative and postoperative blood chemistry values in this case, refer to Table 15.

COURSE. After completing the studies recorded, the patient was subjected to the following surgical procedures.

First Stage (May 3, 1951)—Exploratory Celiotomy, Portal Venography, Ligation of the Portal Vein, Cholecystostomy

With the patient under intratracheal cyclopropane, the abdomen was opened through a generous right upper rectus muscle splitting incision. There immediately presented a large tumor mass some 10 by 9 by 7 cm. lying within the head of the pancreas, invading the lower stomach and duodenum and adherent to the gallbladder. The entire mass was freely movable, there were no regional lymph nodes, the liver was without evidence of metastatic tumor. A gross diagnosis of cancer of the head of the pancreas was made.

A portal venogram was performed by catheterizing a small vein in the upper jejunal mesentery with a polythene tube. Through this, 40 ml. of 35 per cent Diodrast was injected. The film obtained was interpreted as normal. The pressure in the superior mesenteric vein was 12 cm. of saline.

examination of the portal venogram, it seemed obvious that the portal vein was palpably involved.

Here, then, was a patient known to have incurable cancer (melanoma) and almost surely having either another metastatic deposit of melanoma or at least an almost equally incurable (pancreatic) cancer. Under these circumstances, it seemed justifiable to attempt to resect her portal vein. This structure was

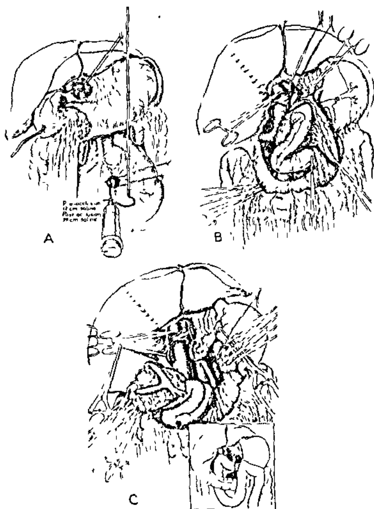


Fig 103 M B N Y H #425 559 Radical pancreaticoduodenectomy with resection of the portal vein A First stage Ligature of portal vein and cholecystostomy B Second stage Details of resection and reconstruction of the enteric canal The immediate postocclusion pressure of 39 cm had fallen to 28 cm of saline fourteen days later. C Second stage Details of resection and reconstruction of the enteric canal (From Child et al Surg, Gynec. & Obst, vol 94 1952)

patient's right of the entrance of the inferior mesenteric vein into the splenic. The entire specimen was then easily dislocated downward and removed after division of the superior mesenteric vein, the inferior pancreaticoduodenal artery, the lateral duodenal peritoneum, and the jejunum at a point 5 cm. distal to the ligament of Treitz. After removal of the tumor and its adnexa, the field of operation was dry. The enteric canal was reconstructed by a retrocolic end-to-end pancreaticojejunos-



Fig 102 M B N Y H #425,559 This venogram was taken two weeks after sudden and complete occlusion of the portal vein and just prior to resection of this vessel together with a large metastatic melanoma of the head of the pancreas (From Child et al Surg, Gynec & Obst, vol 94, 1952)

tomy, an end-to-side mucosa-to-mucosa choledochojejunostomy, and an antecolic gastrojejunostomy. There was no undue bleeding in the course of performing any of these anastomoses. Two cigarette drains were placed down to the pancreatic bed and brought out through the lateral aspect of the transverse incision. The abdominal wound was closed with through-and-through silver wire stay sutures and the various layers of the abdominal wall with chromic #00. The skin was closed with interrupted sutures of fine silk. Supported by 600 ml of 5 per cent glucose in isotonic saline, and 2500 ml of whole citrated blood, this patient withstood the procedure well. Operating time was five

of the pancreas The spleen is submitted separately Lying within the head of the pancreas and obviously involving several of the regional nodes is a tumor measuring 10 by 9 by 7 cm This is yellowish white in color with several areas of dark bluish black The tumor invades the distal stomach, the duodenum, the lower common duct, and the wall of the gallbladder The portal vein is surrounded by tumor, but actual invasion cannot be identified. Upon microscopic section of numerous blocks of tissue removed from the tumor and surrounding structures, there are seen large sheets of basophilic cells whose nuclei vary widely in size and shape Mitotic figures are scant In many areas the tumor is necrotic, while in others it is viable and appears to be actively growing The examined lymph nodes contain much tumor The spleen is congested Diagnosis was malignant melanoma, metastatic

FOLLOW-UP This patient has been followed at frequent intervals since her discharge from the hospital On none of her return visits has she tendered any significant complaints Her weight has remained constant at 120 pounds Her appetite has been good, her bowels regular, and she has remained free of abdominal pain She was seen in September of 1952, sixteen months after operation Esophagograms performed six months and twelve months after operation failed to reveal any evidence of esophageal varices If this patient indeed has portal hypertension, it is not reflected in her esophagograms (Fig 104) *

TWO-STAGE PANCREATICODUODENECTOMY WITH RESECTION OF THE PORTAL VEIN FOR PRIMARY CARCINOMA OF THE DUODENUM

Case #2—J W —N Y H #475,969—Age 67 Years Admitted September 12, 1951 Discharged November 2, 1951

HISTORY This sixty-seven-year-old Negro postal clerk was admitted with a chief complaint of shortness of breath of four months' duration He was, however, without gastrointestinal symptoms

PHYSICAL EXAMINATION Negative

LABORATORY DATA On admission, the hemograms revealed a severe hypochromic anemia, and his stools were consistently positive for blood Upon roentgen visualization with barium, a large ulcer was demonstrated in the duodenum This was believed by the roentgenologist to be either a primary duodenal cancer or an ulcerating lesion secondary to carcinoma of the pancreas The serum bilirubin was 0 5 mg per 100 ml After numerous transfusions, the patient was subjected to the following operative procedures

* At present (Oct 12, 1953 28 months after operation) this patient is alive but as far as can be determined clinically is suffering terminally from extensive metastatic melanoma

hours. Figure 103 A, B, and C illustrates the various steps in this two-stage operation

SECOND STAGE POSTOPERATIVE COURSE This postoperative period was again unremarkable. The drains were removed on the sixth and ninth days after operation. The temperature never rose above 37.6 degrees centigrade, and the serum bilirubin promptly fell to normal The patient was taking a general diet



by the sixth day after operation and was discharged on the thirtieth and twenty-third postoperative days respectively with

corded in Table 16

EXAMINATION OF THE SPECIMEN The specimen was examined by Dr John Pearce, and his report is summarized as follows

The specimen consists of the lower third of the stomach, the entire duodenum and upper 5 cm. of the jejunum, the portal and superior mesenteric veins, the gallbladder and cystic and common ducts, and the uncinate process and most of the body

vein was divided 1 cm upon the splenic side of the junction of this vessel with the portal vein The entire specimen was dislocated downward and to the patient's right After dividing the inferior pancreaticoduodenal artery and the peritoneum constituting Treitz ligament, the terminal duodenum and proximal jejunum were mobilized



Fig 105 J W N Y H #475,960 This venogram was obtained two weeks after acute occlusion of the portal vein This shows practically complete thrombosis of the portal and superior mesenteric veins The radio-opaque material has backed up into the branches of the superior mesenteric vein and outlines an arcade of upper jejunum

At this point as clamps were placed across the superior mesenteric vein, it became obvious that the portal vein, the splenic stump, and a good portion of the superior mesenteric veins were filled with solid thrombus This obviously accounted for the failure of the pressure to fall and for the unusual venogram Because this thrombotic process involved all veins of about the upper third to one half of the jejunum, 70 cm of this structure were resected The proximal jejunum was passed through the defect in the mesocolon and an end to end pancreaticojejunostomy performed A choledochojejunostomy was constructed in the end to-side position An antecolic gastrojejunostomy completed reconstruction of the enteric canal A tube was

First Stage (October 6, 1951)—Exploratory Celiotomy, Revealing a Carcinoma of the Descending Duodenum; Portal Venography, Ligation of the Portal Vein

The peritoneal cavity was entered through a generous oblique incision extending from the left mid-costal margin across both rectus muscles toward the right iliac crest Upon opening the peritoneum a napkin-ring like tumor of the descending duodenum was immediately identified. The common duct was dilated to a diameter of 2 cm There were no regional or distant metastases The tumor invaded the head and uncinate process of the pancreas and upon palpation was adherent to the portal vein A portal venogram was performed revealing dislocation and angulation of this structure toward the left. The inner border of the angulation appeared somewhat irregular. It was concluded that the portal vein was probably involved in the tumor mass The pressure in the portal vein was 16 cm. The portal vein was doubly ligated at the porta hepatis. Following ligature of this vessel, the pressure in the left brachial artery fell from 130/60 to 80/60 Here it remained for ten to fifteen minutes and then rose to stabilize at 110/60 Following portal occlusion, the pressure in the portal vein rose to 28 cm. of saline. The abdomen was closed, and the patient returned to his room

FIRST STAGE POSTOPERATIVE COURSE His postoperative course was uneventful The patient was taking a soft diet on the fifth postoperative day and was returned to the operating room on the tenth postoperative day for the second-stage operation.

Antecolic Gastrojejunostomy

105) There was no filling of the portal, superior mesenteric, or splenic veins Pelvic anastomotic channels, which were a feature of the first patient, were not visualized. In spite of the fact that the portal pressure did not fall and that pelvic collaterals could not be demonstrated, the decision was made to proceed with the operation The spleen was removed in the hope that this would reduce the high splanchnic pressure There was no change. The duodenum and head of the pancreas were freed laterally, and the common duct and portal vein divided The stomach was transected at the junction of the lower and middle thirds. The pancreas was divided in its mid-body. The splenic

legs and began to lose weight Two weeks later, his stools became somewhat light in color Two and one half months before admission, he had a suprapubic prostatectomy following nearly three years of urinary symptoms He received a transfusion after the operation While he was in the hospital, dark urine and persistent clay-colored stools were first noted with certainty as a *persistent symptom These symptoms continued after dismissal*, and his personal physician believed there was obstruction of the bile flow from the liver and advised operation which the patient refused The physician later reported to The New York Hospital that he thought the patient probably had carcinoma of the pancreas During the period immediately before admission to this hospital, itching increased, and signs of jaundice became more marked

About ten years earlier, the patient had been told that he had an enlarged heart, but regular examination had not shown further changes, and his only symptom was some shortness of breath He drank a half glass of wine with his lunch and dinner, but no other alcoholic beverages

PHYSICAL EXAMINATION The patient was markedly icteric

bladder, a rounded mass 5 to 6 cm in diameter was felt The spleen extended one fingerbreadth below the left costal margin and, like the liver, was firm but not tender

8800 X-rays of the esophagus, stomach, and large bowel were negative A chest film showed an enlarged heart

First Stage (April 29, 1952)—Exploratory Laparotomy, Ligation of the Portal Vein, Cholecystojejunostomy—Roux Y Type

An upper abdominal oblique incision roughly 20 cm in length was made This began at the tip of the left ninth costal cartilage and extended across the abdomen parallel to the right costal margin The incision was carried down to the subcutaneous tissue, all bleeders being clamped and tied with fine silk ligatures. The wound was draped with laparotomy pads The anterior *rectus sheath was divided as were the underlying rectus muscles*, all bleeders being clamped and tied with fine silk The peritoneum was then incised for the length of the wound The falciform ligament was divided between Kelly clamps and transfixed with fine silk transfixion sutures

Palpation of the intra abdominal contents revealed the liver to be markedly *enlarged, extending approximately three finger-*

inserted in the gallbladder and brought out through a stab wound in the right flank. The abdominal wound was closed with through-and through silver wire stay sutures. Five cigarette drains were placed down to the area denuded of peritoneum and brought out through the right angle of the wound between the sutures Because of the high portal pressure, this man lost large amounts of blood during the procedure and required 4500 ml. for replacement. At the closure of the abdomen, however, the operative site was dry, and the patient's blood pressure was 140/80 and 86 respectively Operating time was seven hours

PATHOLOGICAL DIAGNOSIS. Carcinoma of the duodenum without regional metastases

SECOND-STAGE POSTOPERATIVE COURSE. His postoperative course was unremarkable By the twenty-first day after operation, he was up and about and taking a general diet. The only detectable abnormalities were a persistently elevated alkaline phosphatase ranging around 15 and a transiently elevated cephalin flocculation He was discharged twenty-seven and seventeen days postoperatively

an

we

portal hypertension. On December 17, 1951, an esophagogram failed to reveal varices. In January, 1952, he began to improve. His appetite returned, he felt stronger, but he continued to have light yellow and sometimes fatty stools. The latter were malodorous, loose, and at times looked like butter. When last seen

sively diminished in number so that he has one movement a day. There is still some fat in the stool, but this has diminished

he is

. The

t *

TWO-STAGE PANCREATICODUODENECTOMY WITH RESECTION OF THE PORTAL VEIN FOR CARCINOMA OF THE HEAD OF THE PANCREAS

Eight months before admission, he began to have occasional episodes of rather vague nausea, but he did not vomit Four months before admission, he noted itching of the hands and

* On Oct 12, 1953, two years after operation, this man is alive and well without evidence of recurrent tumor.

in layers using four double medium silk stay sutures through the anterior rectus sheath, rectus muscle, posterior rectus sheath, and peritoneum. The peritoneum was reapproximated with a continuous 0 chromic catgut suture. The anterior rectus sheaths were reunited with interrupted medium silk sutures, and the skin was closed with interrupted end-on mattress sutures of fine silk.

FIRST STAGE POSTOPERATIVE COURSE. The postoperative course was essentially benign. A Levin tube was placed in the stomach, and the patient received penicillin, dihydrostreptomycin and intravenous fluids, and was as rapidly as possible advanced to a general diet. On the seventh day after operation, the wound was well healed and the sutures were removed.

Second Stage (May 8, 1952)—Radical Pancreaticoduodenectomy with Resection of the Portal Vein, End-to-End Choledochojejunostomy, Antecolic Gastrojejunostomy

The previous abdominal incision was opened, and the peritoneal cavity briefly surveyed for evidence of metastasis which might have taken place since the previous operation. A portal venogram was performed by threading a small catheter into a branch of the superior mesenteric vein and injecting 50 cc. of 70 per cent Diodrast (Fig. 106). This beautifully outlined the extrahepatic portal system, demonstrating that most of the collateral circulation had taken place through the pelvic veins. The pressure in the intervening ten days had fallen to 24 cm. of saline. Believing that it was safe to operate through a venous field of this pressure, we proceeded with the operation.

The first maneuver was to divide the common duct as near the porta hepatis as possible and then to divide the portal vein. At this point, the hepatic artery which was very close to the primary tumor was dissected free from the surrounding structures and skeletonized outlining the junction of the hepatic with the gastroduodenal artery. This artery was divided flush with the hepatic artery, and the small nib distal to the tie sent for frozen section. Since there was no tumor apparent in the arterial wall, we proceeded with the dissection, carrying it toward the left side of the patient, removing as much of the node bearing hepatoduodenal and hepatogastric ligaments as possible. The stomach was then divided at its mid point and the pancreas divided between clamps far out on its tail, just at the junction, perhaps, of the body and tail. About 3 to 4 cm. of the tail of the pancreas was left in situ. This was divided between clamps.

Dissection was then continued until the splenic vein and splenic artery were identified. The splenic artery was carefully freed and left intact. The splenic vein, however, was divided. This then permitted mobilization of the entire specimen caudad. As far as could be determined, there was no direct invasion

breadths below the right costal margin and below the xiphoid

distended and

ickened appre-

The stomach

and duodenum appeared normal. Palpation of the retroperitoneal structures and common duct through the foramen of Winslow revealed a hard tumor mass, roughly 4 by 3 by 2 cm., at the superior border of the head of the pancreas and extending

could not be palpated in the gallbladder or in the common duct.

A purse-string suture of fine silk was placed in the fundus of the gallbladder and the contents of the gallbladder aspirated with a trocar Exploration of the hepatic artery, portal vein, and common duct revealed the tumor mass to be situated just inferior to the course of the hepatic artery. It appeared to envelop the right gastroduodenal artery and to angulate the hepatic artery downward As was stated previously, it was noted to obstruct almost completely the common duct at this level and to cause considerable angulation and puckering of the wall of the duct At this point, a small branch of the superior mesenteric vein was catheterized The initial portal pressure was 22 cm. of saline.

A portal venogram was then done, and this showed angulation of the portal vein but no definite evidence of invasion It was felt that because of the patient's severe jaundice and the fact that the portal vein was distorted considerably from its normal anatomical course and position, a two-stage procedure for resection of this tumor mass was indicated. Therefore, it was felt that in the first stage ligation of the portal vein and a Roux Y type of cholecystojejunostomy should be performed. These procedures were carried out as follows:

The portal vein was dissected free from surrounding structures at a point 3 cm superior to the tumor mass. It was occluded for a fifteen minute period, during which time the patient's blood pressure fell slightly Ligation of the portal vein was believed safe, and therefore a double medium silk ligature was placed about the portal vein and tied. A cholecystojejunos-

clamped with Kocher clamps and divided. The distal end of the severed jejunum was then brought up and anastomosed to the fundus of the gallbladder. An adequate lumen was obtained. The proximal end of the severed jejunum was then sutured in an end-to-side fashion to the jejunum some 30 cm distal to the cholecystojejunostomy anastomosis. The wound was then closed

in layers using four double medium silk stay sutures through the anterior rectus sheath, rectus muscle, posterior rectus sheath, and peritoneum The peritoneum was reapproximated with a continuous 0 chromic catgut suture. The anterior rectus sheaths were reunited with interrupted medium silk sutures, and the skin was closed with interrupted end-on mattress sutures of fine silk.

FIRST STAGE POSTOPERATIVE COURSE The postoperative course was essentially benign A Levin tube was placed in the stomach, and the patient received penicillin, dihydrostreptomycin and intravenous fluids, and was as rapidly as possible advanced to a general diet On the seventh day after operation, the wound was well healed and the sutures were removed

Second Stage (May 8, 1952)—Radical Pancreaticoduodenectomy with Resection of the Portal Vein, End-to End Choledochojejunostomy, Antecolic Gastrojejunostomy

The previous abdominal incision was opened, and the peritoneal cavity briefly surveyed for evidence of metastasis which

extrahepatic portal system, demonstrating that most of the collateral circulation had taken place through the pelvic veins The pressure in the intervening ten days had fallen to 24 cm of saline Believing that it was safe to operate through a venous field of this pressure, we proceeded with the operation.

The first maneuver was to divide the common duct as near the porta hepatis as possible and then to divide the portal vein At this point, the hepatic artery which was very close to the primary tumor was dissected free from the surrounding structures and skeletonized outlining the junction of the hepatic with the gastroduodenal artery This artery was divided flush with the hepatic artery, and the small nib distal to the tie sent for frozen section Since there was no tumor apparent in the arterial wall, we proceeded with the dissection, carrying it toward the left side of the patient, removing as much of the node bearing hepatoduodenal and hepatogastric ligaments as possible The stomach was then divided at its mid point and the pancreas divided between clamps far out on its tail, just at the junction, perhaps, of the body and tail About 3 to 4 cm of the tail of the pancreas was left in situ This was divided between clamps

Dissection was then continued until the splenic vein and splenic artery were identified The splenic artery was carefully freed and left intact The splenic vein, however, was divided This then permitted mobilization of the entire specimen caudad As far as could be determined, there was no direct invasion

of the superior mesenteric artery. This portion of the field was left and attention was directed to the base of the mesocolon Here Treitz's ligament was entirely destroyed and the upper jejunum mobilized by dividing the proximal 4 to 5 cm of its mesentery between clamps. The proximal jejunal stump was closed beneath an inverting purse string suture.

Turning to the upper abdomen, where dissecting was continued, we freed the uncinate process from around the neigh-



splenic and inferior mesenteric vessels are nicely seen.

borhood of the superior mesenteric artery We believed that we were entirely free of tumor, however, as we descended posteriorly, we were discouraged to feel one or two nodes that seemed to lie between the aorta and the inferior vena cava These could not be dissected free with the specimen, and, as time was pressing, had to be left in place At this time, we were able to identify the inferior pancreaticoduodenal artery at its origin. Following division of this vessel, the entire specimen was readily mobilized and after dividing the duodenocolic ligament and omentum, the entire mass was removed The upper abdomen was therefore bare of the distal third of the stomach, the

entire head and body of the pancreas together with the attached portal vein, the terminal two thirds of the extrahepatic common duct, and a segment of an intramural portion of the cystic duct All bleeding was controlled, and there was no evidence of excessive capillary ooze from any of the sites of resection

In reconstruction of the enteric canal we elected simply to close the pancreatic stump, relying on extra pancreatic tissue to supply the necessary enzymes for pancreatic digestion. This was closed first with interrupted mattress sutures and then with a second layer of deep U sutures in the hope that we could prevent the formation of a fistula The continuity of the enteric canal was then reestablished by implanting the combined cystic and common ducts into the open end of the jejunum as an end to end choledochojejunostomy This was in a mucosa to-mucosa suture, performed with 0000 chromic catgut and serosa-to-serosa with interrupted sutures of fine arterial silk The jejunal loop used for this anastomosis was brought up through a rent in the antecolic position At the close of the procedure, the gastrojejunostomy, the end to end choledochojejunostomy, the stump of the pancreas, and the entire bed of resection appeared dry and in good condition The abdominal wound was then closed

patient withstood this long and arduous operative procedure well

PATHOLOGICAL DIAGNOSIS Carcinoma of the pancreas metastatic to regional lymph nodes and invading the adventitia of the portal vein

SECOND STAGE POSTOPERATIVE COURSE For eight days after operation, the course was benign Dressings were changed daily, and only a moderate amount of serosanguineous drainage oc

temperature rose to 38 5 degrees centigrade, and pretibial edema appeared Digitalin was given to prevent circulatory failure, and medical treatment instituted. Twelve days after the episode had begun, he was much improved in all respects and all medication except diuretics was discontinued Rales in the bases of the lungs improved, and jaundice decreased steadily He was discharged in relatively good condition seven weeks after admission and five weeks after the first operation

FOLLOW UP On the patient's first visit to the clinic, June 17, 1952, his diarrhea was decreasing and only slight icterus of the sclera remained He was subsequently seen at the clinic at about two week intervals, and improvement continued quite steadily though somewhat slowly On August 26, 1952, four months

of the superior mesenteric artery. This portion of the field was left and attention was directed to the base of the mesocolon. Here Treitz's ligament was entirely destroyed and the upper jejunum mobilized by dividing the proximal 4 to 5 cm. of its mesentery between clamps. The proximal jejunal stump was closed beneath an inverting purse string suture.

Turning to the upper abdomen, where dissecting was continued, we freed the uncinate process from around the neigh-



splenic and inferior mesenteric vessels are nicely seen.

borhood of the superior mesenteric artery. We believed that we were entirely free of tumor; however, as we descended posteriorly, we were discouraged to feel one or two nodes that seemed to lie between the aorta and the inferior vena cava. These could not be dissected free with the specimen, and, as time was pressing, had to be left in place. At this time, we were able to identify the inferior pancreaticoduodenal artery at its origin. Following division of this vessel, the entire specimen was readily mobilized and after dividing the duodenocolic ligament and omentum, the entire mass was removed. The upper abdomen was therefore bare of the distal third of the stomach, the

right upper quadrant and flank soreness at this time and a sensation of something hard in this region Her appetite failed and food caused nausea, but she vomited only once A progressively deepening jaundice developed, with light stools and dark urine, and she became increasingly weak. Her local physician pre

protein and low fat diet. However, her abdomen began to swell and her skin to itch. Inquiries were made locally, and it was decided to bring her to this hospital for further investigation She was referred from the Bayamon District Hospital, Bayamon, Puerto Rico, with a diagnosis of jaundice

PHYSICAL EXAMINATION On admission to this hospital, the patient was a well developed woman, deeply jaundiced, but not in acute distress Her blood pressure was 120/75 There was tenderness in the subxiphoid and right subcostal area, but no mass could be felt Some telangiectases were scattered over her body. Preliminary examinations and consultation justified a diagnosis of obstructive jaundice, probably caused by malig-

LABORATORY DATA Urine was positive for bile Gastrointestinal x rays revealed no intrinsic lesion of the esophagus, stomach, or duodenum There was non visualization of the gallbladder

COURSE After completion of these studies, the patient was subjected to the following operations

First Stage (August 20, 1952)—Exploratory Celiotomy, Portal Venogram, Roux Y Cholecystojejunostomy

portal pressure was measured and found to be 22 cm of saline, distinctly elevated The portal venogram revealed a large defect in the portal vein, believed to represent infiltration with tumor (Fig 107A) Furthermore, there were rather extensive collaterals as revealed by the portal venogram

The problem then arose as to what our procedure should be Because of her deep jaundice, the patient was considered a poor operative risk, and therefore decompression of the biliary tract with a Roux Y cholecystojejunostomy was selected. Because of

after his first operation, he reported that he had returned to work for two or three hours a day On September 8, 1952, four months and a half after operation, he was asymptomatic except for a

small, slightly tender, oval masses were present along the right angle of the incision These were believed to represent metastases. The liver was definitely nodular. Edema of the ankles was also observed. On October 6, 1952, he was, however, still feeling quite well but was passing several loose stools a day No change in his general status was evident until November 17, 1952, when he reported considerable backache. The abdomen was protuberant at this time, and there was some ascites. The liver extended 4 to 5 fingerbreadths and the spleen 2 fingerbreadths below the costal margin. By December 1, 1952, his appetite was only fair, and by December 15, 1952, the clinical examination

numerous metastases On subsequent visits he continued to fail, and on February 15, 1953, he was at home in bed, in terminal condition The suggestion was made that a visiting nurse see him once a week to give testosterone and Mercuhydrin This patient died in May 1953, one year after operation.

RADICAL PANCREATICODUODENECTOMY WITH RESECTION OF THE PORTAL VEIN FOR CARCINOMA OF THE PANCREAS

Case #4—A R —N.Y H. #635,339—Age: 48 Years Admitted: August 13, 1952 Discharged· October 3, 1952

HISTORY. This forty-eight-year-old Puerto Rican woman was admitted to the medical service of this hospital because of nausea and abdominal swelling. She had always been subject to headaches, gas pains, hay fever, poor appetite, low blood pressure, and digestive difficulties. Twenty-seven years before admission, she had a brief interval of ankle edema Twenty years before she was admitted she had malaria, and nine years before she was seen here "kidney infection," bilateral flank pain, and a "nervous breakdown" following pneumonia. Twice, twenty-

the present illness. Seven weeks before admission, she noticed a feeling of epigastric fullness and discomfort. She had some

dure well, and after closure of the abdominal wound with interrupted double medium silk stay sutures and continuous

to include the portal vein

FIRST STAGE POSTOPERATIVE COURSE The postoperative course was uneventful except for some abdominal pain She received *transfusions of a total of 1522 cc. of blood* Films of the abdomen failed to demonstrate evidence of any abnormality of the intestinal tract

Second Stage (September 2, 1952)—Radical Pancreaticoduodenectomy, Resection of the Portal Vein

The previous operative incision was opened and after care- ... adhesions, a vein in the upper

tient did not conform to our postulate that the portal pressure would fall to within the range of 20 cm of saline We had, of course no choice but to proceed, even though the pressure was at th

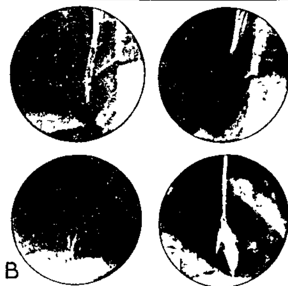
uppe

previously placed about the portal ve

Dissection was then carried up the gallbladder bed, releasing the gallbladder and its associated cholecystojejunostomy The lateral peritoneal duodenal reflection was incised and the entire head of the pancreas, the common duct, and the portal vein mobilized toward the left side of the patient We then divided the stomach at the junction of its lower and middle thirds, the pancreas at the junction of its outer and middle thirds, and

teric canal that was possible This consisted of an end to end choledochojejunostomy. Then the jejunum was swung anterior to the colon and a gastrojejunostomy performed. We eliminated





inferior mesenteric and the retropancreatic veins (See text.)

geal varices [illegible]
known. (See text.)

she did not vomit She was discharged on October 29, 1952, improved, to the care of her local physician in Puerto Rico

FOLLOW UP. From time to time, A R 's physician in Puerto

the presumption is that she is suffering from recurrent tumor. Esophagograms (Fig 107B) were obtained six months after operation and failed to reveal any evidence of varices.*

In addition to these cases, three other patients have been recorc from other clinics in whom the portal vein has been either whc or partially resected At the 1950 meeting of the American Surgi Association, Dr W Barclay Parsons reported a patient in whor portion of the portal vein was resected because of obvious invas by tumor In the same year, Dr E Cooper Person and Dr. Jc Divine, Jr, reported as a personal communication to Child t they, too, had resected the portal vein in a patient with a prim pancreatic cancer. Both of these surgeons expressed the belief t in these patients the portal vein had been obstructed for a su ciently long period of time for collaterals to have become at le partially established The third reported case is that of Dr Willi V McDermott who successfully resected the portal vein after est lishing a shunt between the superior mesenteric vein and the v cava.

It is obvious from these reports that the portal vein can be sected Pancreaticoduodenectomy can now be regarded as a m radical operation than it has heretofore been How useful this ad maneuver will prove to be has as yet to be determined That its plication will be extremely limited seems certain Only the patient whose pancreatic cancer is limited to the head or uncin process but invades the portal and superior mesenteric veins car the foreseeable future be considered a candidate for this operati

At the present time, what generalizations can be drawn with reg to the technique of removing the portal vein in a block with head of the pancreas? In the first place, resection after implantat of the superior mesenteric vein into the vena cava must be con ered the procedure of choice for, if it can be accomplished, operation is performed in one stage and the patient is protec *from the development of postoperative portal hypertension.* In second place, complete portal obstruction must be considere

* Fourteen months after operation this patient is reported to be well, ing recently undergone an exploratory celiotomy with lysis of adhesions acute small bowel obstruction At the time of this operation her surgeon unable to detect any evidence of recurrent tumor

the pancreaticojejunostomy in this patient because the tumor had so obstructed the pancreatic duct that this organ was large, edematous, and friable, and would not have been suitable for any form of end-to end anastomosis Three large cigarette drains were placed down to the stump of the pancreas and incorporated in them was a catheter for continuous suction. At the close of the procedure, the anastomosis appeared in good condition. The bowel by this time had almost regained its normal color, and although the pressure was not measured, there was no excessive venous ooze.

The abdominal incision was closed about the drains, employing several wire stay sutures throughout and interrupted catgut

SECOND STAGE POSTOPERATIVE COURSE. In general, the postoperative course was benign There was persistent large to moderate serosanguineous drainage for about two weeks, and drainage from a sinus following removal of the drains for another three weeks. The patient complained of considerable pain. Because blood proteins were low, she received transfusions totalling 2500 cc. and 1300 cc of plasma. Films of the abdomen eight days after operation did not indicate the presence of intestinal obstruction A second study of the abdomen nine days later was also negative Gastrointestinal and small intestinal studies twenty-four days after operation showed a well functioning gastrojejunostomy Seven weeks after admission and one month after operation, the patient was discharged to a convalescent home.

FOLLOW-UP. On October 11, 1952, eight days after discharge, it was reported that the patient had a temperature of 101 to 102 degrees, pus in her urine, and had, on the previous day, vomited greenish fluid and blood and passed bloody stools. She also experienced shaking chills.

SECOND ADMISSION. On the day this report was received, the patient was readmitted to this hospital On admission, she was experiencing severe pain in her back and abdomen and severe headache, and there was evidence of blood in her stools She was thin, and her blood pressure 94/56. She continued to vomit and passed bloody stool for one day after admission. She was given two transfusions of blood of 500 cc each and placed on penicillin and dihydrostreptomycin therapy. Gastrointestinal and small bowel x-ray studies on October 20, 1952, were negative A sinus tract extended 2¾ inches deep from the area of the incision. By October 23, 1952, twenty two days after admission, stool examinations indicated that bleeding had stopped Abdominal pain was gradually controlled Nausea persisted, but

CHAPTER 16

Preoperative and Postoperative Water, Electrolyte, and Protein Balance in Patients with Cirrhosis

EARLIER in this monograph (Chapter 10), an effort was made to summarize concisely some of the current concepts of the relationship of the normal and diseased liver to control of body water, electrolyte, and protein It is the purpose of this section to try to interpret some of these concepts in terms of the preoperative and postoperative care of the patient with cirrhosis The basis for these interpretations is The New York Hospital's experience with 30 patients operated upon for portal hypertension secondary to cirrhosis of the liver In all of these, a portacaval or splenorenal shunt was performed which successfully reduced portal pressure to safe levels By far the majority of these patients were operated upon in a state of reasonable hepatic compensation Six, however, were extraordinarily poor-risk patients in whom operation was performed as a desperate attempt to protect them from further massive hemorrhages

It would indeed be rewarding were it possible as a result of these carefully controlled studies to establish a number of infallible rules, observation of which would insure success in carrying one of these patients through his operative experience Unfortunately, this is not the case The problems which arise are largely unpredictable and must be solved as the occasion demands

The major handicap, of course, to carrying a patient with advanced liver disease through a major surgical experience resides in the fact that basic knowledge of the causes of edema, ascites, and abnormal sodium and protein metabolism, and of the effects of hepatic disease on renal function, is imperfect Even today, it is far from clear just why the patient with cirrhosis handles water and electrolytes differently from the normal patient Why postoperatively one patient with a given degree of cirrhosis will develop massive ascites, while another with apparently comparable degrees of liver damage does not, is oftentimes quite inexplicable The treatment of postoperative

hazardous operation, for it is probable that in a few patients, severe degrees of portal hypertension may develop and subject them to all the risks which this state entails. The advantage, however, of the two-stage operation is well represented in the four cases operated upon at The New York Hospital. In each instance, the tumor extended so far down upon the superior mesenteric vein that preservation of a section of this vessel free of cancer seemed quite impossible. It is probable that McDermott's operation will have to be reserved for the rare patient whose tumor lies along the upper border of the pancreas and does not extend downward toward the base of the mesocolon.

As evidenced by Parsons' and by Person's patients, the portal vein can be resected in one stage provided the portal blood flow has been compromised for a sufficiently long time to allow the establishment of a venous collateral connecting the portal to the systemic venous systems. How to determine that the collaterals have formed must at this time be a matter of conjecture. Several maneuvers, however, might prove helpful. For instance, a portal venogram, if it showed complete or even extensive obstruction of the portal vein, might be considered evidence that adequate collaterals were present. If at the same time portal pressure was elevated and did not rise further upon complete obstruction of the portal vein at the hilus of the liver, it could be safely assumed that adequate collaterals were indeed present. However, if the portal pressure rose substantially over 30 cm. of saline after complete portal occlusion, it would have to be considered questionable whether it would be safe to proceed without a preliminary period of complete occlusion of the portal vein.

It is improbable that the final answers to these physiological problems can be had at this time. Only by persistent effort will it be possible to standardize a technique whereby the portal vein can be resected safely, and only by careful follow-up studies will it be determined whether radical pancreatectomy is worth-while at all. For instance, if the salvage rate proves to be no higher than it is at present and if the patients live only to succumb to hemorrhage from [illegible] have been accomplished by [illegible] this procedure does prove to [illegible] surgical world may then turn its attention to the resection of the superior mesenteric artery.

either preparing a patient with cirrhosis for operation or carrying him successfully through his surgical experience It is well recognized, for instance, that a patient whose serum albumin level is 3 grams per 100 ml or lower will tolerate any operation poorly Since it is frequently impossible to invest the time to see whether this abnor-

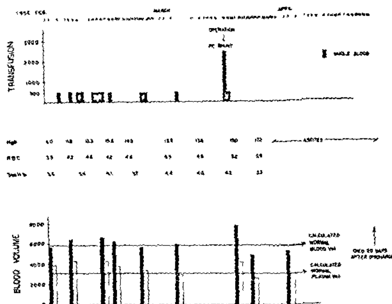


Fig 108 J McE N Y H #620,310 Advanced cirrhosis (Portacaval case #17) Preoperative preparation, replacement during operation, and post operative management In this patient, ascites was a feature of the preoperative and postoperative course This was gradually corrected by whole blood transfusions and salt and water restriction (see Figs 112 and 113) At the time of operation, his blood and plasma volumes were overexpanded in spite of reasonably normal hemoglobin, red blood count and serum albumin levels Apparently replacement therapy was effective during and immediately after operation Postoperatively his serum albumin level fell steadily, however, and this man died at home twenty days after discharge His family reported that he acquired ascites massively, was totally anuric and in coma at the time of his death at home This patient undoubtedly falls into that group of patients with cirrhosis who can be maintained in a hospital As soon, however, as they depart and are "upon their own" they rapidly pass into hepatic failure and die Portal decompression is hardly worth while in such patients

mality can be corrected by dietary means, advantage must be taken of any method which will elevate the concentration of this essential in the blood to 3 5 to 4 0 grams per 100 ml This can be accomplished temporarily at least by the use of human albumin, plasma, or multiple transfusions In Figures 108, 109, 110, and 111 are demonstrated

ascites and edema and renal failure becomes, therefore, a problem which must, to a large degree, be individualized.

tha

anc

and often proved to be fatal postoperative complications. With the studies that have been directed in recent years toward a better understanding of water, electrolyte, and protein needs of patients with normal and abnormal livers, a number of the mysteries of the postoperative course of the patient with cirrhosis have been clarified Although many problems still remain to be solved, the surgeon today is in a better position than ever before to deal effectively with at least the majority of the metabolic disorders appearing in response to the stress of operation What metabolic defects, then, characterize the patient with cirrhosis, and how may reasonable efforts be made to correct them?

The most important of these disorders are low serum albumin, decreased osmotic pressure within the vascular system, increased sodium retention, and excesses of a presumed, though as yet ill defined, antidiuretic substance As information about these several abnormalities has been accumulated, there has appeared reason to doubt that edema, ascites, and oliguria are solely the manifestations of a deranged balance between capillary hydrostatic pressure and intravascular colloid osmotic pressure. As valid as Starling's hypothesis has proved to be for the normal individual, it appears defective in explaining why ascites collects in the peritoneal cavity of patients with cirrhosis

Serum Albumin Level

For years the portal hypertension generally accompanying cirrhosis was thought to be the important factor in depleting serum albumin reserves Today this is known not to be the only factor Not only is the diseased liver unable to fabricate this substance in normal amounts, but in addition, intrahepatic lymphatic block is also believed to contribute importantly to the formation of ascites Defects in serum albumin levels have been shown to play an important role in abnormal water retention, and the results of their correction are valuable. In some patients with cirrhosis, intensive replacement therapy has been associated with marked diuresis; in others favorable responses have failed to appear Furthermore, spontaneous diuresis can occur in patients with low serum albumin levels On the other hand, even massive ascites appears in patients with cirrhosis during periods of normal or near normal albumin levels

Despite these conflicting evidences, blood plasma and salt-poor albumin have proved clinically to be important therapeutic agents in

Salt Retention

That salt is retained in the patient with cirrhosis and ascites and edema is well known In our own laboratory, sodium space and total body water determinations have recently been completed upon 7 patients with moderately advanced cirrhosis but without edema or ascites In all of these, total body water as percentage of body weight

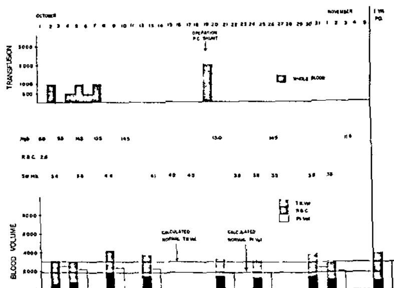


Fig 110 G N N Y H #484,088. (Portacaval case #14) Preoperative preparation, replacement during operation, and postoperative management in a patient surviving a shunt uneventfully In this patient, the red cell mass was restored preoperatively by means of whole blood transfusions This resulted in a somewhat overexpanded blood and plasma volume which persisted postoperatively and was present a year later This late observation casts some doubt upon the popularly held concept that the overexpansion of blood and plasma volumes seen in patients with cirrhosis is due to the dilated portal venous system In this patient the portal system was adequately decompressed and yet her blood volume did not adjust itself to normal levels These same findings were manifested by the previous patient, Figure 109

was normal In all, the sodium space was slightly expanded compared with the normal The ratio of the sodium space to total body water was slightly elevated, that is, we found an average of 54 per cent compared with our normal of 46 per cent The obvious implication is that in cirrhosis, intracellular water is low Whether this is actually true or not remains to be determined (Gilder et al 1953)

From these studies, the impression has also been gained that in

the course of four patients whose protein deficits were adequately corrected by parenteral means In passing, it must be emphasized that amino acid solutions administered parenterally appear to have little place in the treatment of patients with cirrhosis. Their hepatic defects appear to preclude using these protein building blocks

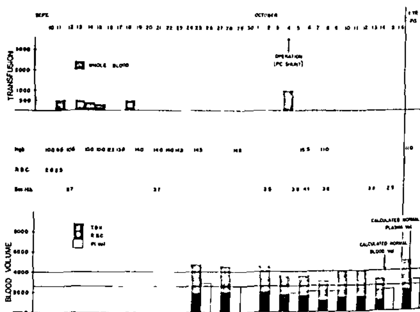


Fig 109 S M N Y H #533,020 Moderate cirrhosis. Preoperative preparation, replacement during operation, and postoperative management in a

to 3 5 grams per 100 ml A year later, her blood and plasma volumes were overexpanded in spite of low hemoglobin

effectively Furthermore, there is some evidence that these substances may be harmful or even toxic to the patient with cirrhosis

The subject of the parenteral use of homologous colloids cannot be left without a note of warning! Since one of the pathological features of the patient with cirrhosis is an overexpansion of his extracellular compartment and his plasma volume, any substance capable of precipitously elevating intravascular osmotic pressure

cirrhosis.

renal tubular mechanism have been predicated In spite of many studies such as these, however, it must be admitted that even today the actual mechanism leading to salt retention is unknown

Restriction of Salt Intake

The knowledge that salt is retained has, of course, led to the widespread use of various salt restricting programs Deprivation has been obtained by dietary restrictions, dietary deletion, and by the use of ion exchange resins It has been well demonstrated that by restricting sodium intake to 25 or so milliequivalents per day, edema and ascites formation can be materially reduced in most patients even with advanced cirrhosis In view of this fact, it becomes important to control most carefully the postoperative administration of sodium-containing solutions A profitable practice during the first several days after operation is that of withholding all salt except that specifically needed to replace routine losses Even here it is better to measure carefully the amount of sodium ion lost in these secretions and replace it milliequivalent for milliequivalent rather than to rely upon gross replacement with isotonic saline

In employing programs which seriously restrict salt intake, a surgeon must ever be on guard against the development of a low serum sodium syndrome Early, this is manifested by weakness, lassitude, nausea, and falling systolic blood pressure, late, by blood pressure at shock levels, partial renal failure, and death The development of this state seems to be avoided by carefully individualizing the treatment of each patient The cirrhotic varies so greatly in his ability to handle salt, not only from patient to patient but in the same patient almost from day to day or week to week, that a routine for all patients may prove extremely hazardous Of particular importance is recognition of the fact that any patient whose serum sodium is being maintained at critical levels may suddenly be thrown into serum sodium depletion by any number of events which in the normal patient might be reasonably well tolerated Hemorrhage, even of small amounts, vomiting, diarrhea, profuse sweating, and paracentesis have all been identified as agents precipitating the patient with low serum sodium levels into a status of serious salt depletion Nor are these obvious mechanisms the only method for producing this undesirable state, an extensive operation, just as a serious burn, may produce such a major expansion of a localized area of interstitial edema as to deplete the serum sodium to seriously low levels This state, should it develop, can readily and immediately be corrected by the administration of 5 per cent sodium chloride solution in the required amount This can be calculated from the

cirrhosis the only way the ratio of total exchangeable sodium to the sodium space can be kept normal is by severely restricting sodium intake When patients were permitted an unrestricted sodium diet, the ratio of total sodium to sodium space became elevated. This, of course, confirms the well known fact that the patient with cirrhosis is unable to maintain a normal extracellular sodium concentra-

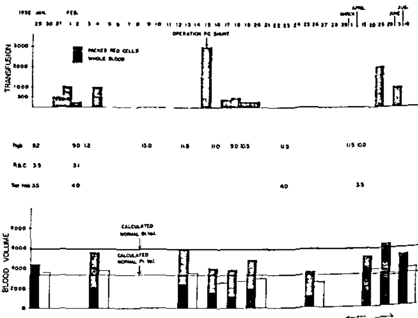


Fig 111. A K N Y H #498,896 Moderate cirrhosis Preoperative prep-

her plasma volume was slightly expanded, but three blood volumes were normal.

tion unless the intake of the ion is restricted More simply stated, the patient with cirrhosis cannot handle sodium normally Wherein his defect lies is not known Such individuals may excrete as little as 1 to 2 milliequivalents of sodium a day in their urine, and it has been shown that the sodium content of their sweat and saliva is also decreased When test loads of salt have been administered, it has been demonstrated that renal excretion of sodium is impaired in spite of normal glomerular filtration and renal blood flow Upon these two bits of evidence, abnormalities in adrenal function and the

be withheld It has been accepted that these substances can be employed effectively in preparing for operation patients whose sodium levels are high Again, care must be exercised so that the mark is not overshot Mercurial diuretics, enhanced or not by ammonium chloride, have long been popular in the control of edema and ascites Unfortunately, in the patient with advanced cirrhosis,

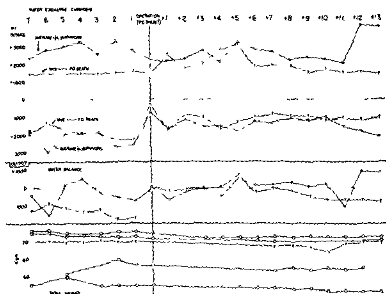


Fig 112 In this chart have been outlined the preoperative and postoperative water exchanges in five patients with cirrhosis Four were relatively well compensated as far as their hepatic reserve was concerned, while one patient was an admittedly poor risk patient and died several weeks after operation It is difficult, indeed, to detect any striking differences in the ability of these five patients to handle water

their effectiveness may be lost As in all diseases for which specific therapy is unknown, ACTH and cortisone have been tried The results, however, in the use of these agents not only have so far been disappointing, but there are hints that they may even be dangerous

In Figures 112 and 113 are graphically represented the courses of several patients with advanced cirrhosis The legends outline appropriately the problems involved In general terms, these clinical studies have been disappointing in so far as they have not revealed any striking defect Nor, it must be admitted, have they provided any important specific leads as to how patients should be managed in

patient's serum sodium level and his estimated extracellular compartment (20 per cent of his normal body weight). Administration should be cautious and its effectiveness can be judged from the clinical response obtained. Isotonic solutions of sodium chloride are, of course, ineffective under these circumstances, for they simply add to the water overload without providing the additional sodium ion required.

TABLE 16

L. De A.—Age 58—N.Y.H. 234,792 — Esophagogastric Hemorrhage
Cirrhosis of Liver — Vomiting
Nephritis (? Mercurial) — Ascites

DAY	WEIGHT KG	ASCITES AND EDEMA	SERUM Na	5% SALINE	URINE Na 24 HRS	WATER Gain	WATER Loss
1	54.3	+	93 mEq/L 96 mEq/L	40 ml q. 1 h.	146 mEq	3200 ml	2400 ml
2	57.0	+	109 mEq/L 120 mEq/L	to a total of	163 mEq	3900 ml	2800 ml
3	57.6	++	139 mEq/L	1650 ml	63 mEq	3750 ml.	2600 ml
4	58.0	+++	132 mEq/L			3600 ml	2750 ml
5	58.3	+++	132 mEq/L		52 mEq	2350 ml	3535 ml
6	59.0	+++	122 mEq/L		190 mEq	3200 ml	2500 ml
11	57.6	+++	133 mEq/L			3500 ml	2250 ml
15	56.0	++	133 mEq/L				
16		—	— HO	ME —	—		

A patient recently treated at the New York Hospital demonstrates this point. L. De A., with advanced cirrhosis, had had his edema and ascites effectively controlled by a low salt regimen. Shortly before admission, he suffered a massive hematemesis, the manifestations of which were well controlled by whole blood transfusions. Within a few hours, however, he became disoriented, vomited, and lapsed into coma. His systolic blood pressure fell from a normal of 180/90 to 88/40 millimeters of mercury. His serum sodium was determined to be 94 milliequivalents per liter. This entire picture was returned to normal by the administration of 1650 milliliters of 5 per cent sodium chloride solution (Table 16).

Other Methods of Control

Recently ion exchange resins have become popular in the management of patients with cirrhosis. The resin used should, of course, be potassium-saturated, and during its use ammonium chloride should

APPENDICES

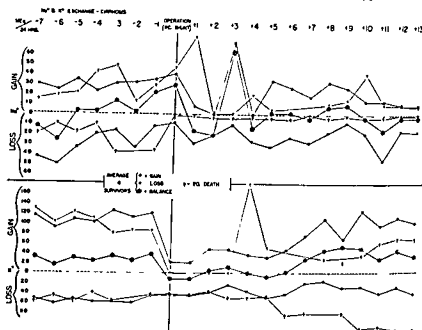


Fig. 113 In this chart are outlined the sodium and potassium exchanges in the same five patients whose water exchanges were outlined in Figure 112 Again, differences are not striking The patient who died postoperatively (designated by a cross) appeared to handle these two electrolytes much as did the survivors, at least as far as could be detected clinically and biochemically

the future. If any generalization is warranted, it is that these patients have reacted to their stressful situations much as would other patients of comparable age and nutritional depletion. In some measure, then, the patient with cirrhosis who is clinically in adequate shape for operation can be relied upon to stand the operation relatively well

APPENDIX 1

Sudden and Complete Occlusion of the Portal Vein in the Macaca Mulatta Monkey

*Animals**

MACACA MULATTA monkeys were obtained from various animal dealers in the vicinity of New York City Animals recently imported from abroad were not used because they were usually much too small for surgical experimentation and all too often developed tuberculosis within a few months after admission to the colony Animals which had been, or were destined to become, residents in one or another of the country's zoos were purchased whenever available Generally these weighed from 15 to 25 pounds In animals of this size, the structures about the pancreas and duodenum were large enough to work upon with relative ease In general these monkeys arrived in the colony in good condition, when undernourished they were usually retained long enough before operation to make sure that they were gaining weight and in good health All animals, immediately upon admission, were tested with tuberculin, and roentgenograms of their chests were obtained Any animals manifesting a positive tuberculin test or showing evidence of pulmonary tuberculosis were never admitted to the colony but were killed immediately For the most part, monkeys were kept in individual cages, although on occasion two animals who had been in the colony three months or more were housed together If an animal became ill during the course of the experiments, it was immediately withdrawn from the colony and placed in isolation, and if it did not recover promptly, it was killed In spite of these precautions, two epidemics of tuberculosis swept the colony, requiring on one occasion the sacrifice of twenty animals and on another fifteen The healthy animals thrived upon an ad

* These generalizations concerning monkeys and their care apply wherever in the following studies these animals have been used as experimental subjects

viscera It has been postulated, therefore, that in these animals (8 per cent of the entire series) the number and size of pre-formed portasystemic shunts were not adequate to permit a sufficient amount of blood to maintain life to be transferred promptly from the portal to the systemic circulation These 6 animals, then, behaved like the dog They are believed to have bled to death into their splanchnic beds Eight sickly and malnourished animals died within a day or two of occlusion of their portal vein, and in retrospect probably

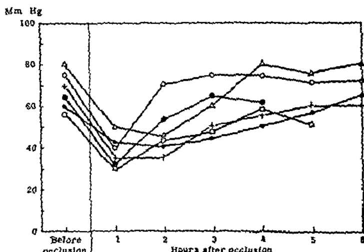


Fig 114 Unlike the dog, an animal in which lethal shock is precipitated by sudden and complete occlusion of the portal vein, the monkey manifests only a transient fall in systemic arterial pressure and survives quite uneventfully

should not have been operated upon One animal died shortly after the intraportal injection of 50 ml of 70 per cent Diodrast, another following ligature of both the portal vein and hepatic artery, and a third of an acute gastric dilatation

The gross mortality in this series, then, is 22 3 per cent If some degree of correction be permitted, only 8 per cent of the deaths appear due directly to portal occlusion

In an effort to discover why this animal, unlike rabbits, cats, and dogs, survives sudden and complete portal occlusion, the following observations have been made

1 SYSTEMIC ARTERIAL PRESSURE In 42 animals the systemic arterial pressure was recorded before and up to six hours after

libitum diet of milk, bread, bananas, oranges, lettuce, carrots, and other vegetables

Methods

All food and water was withheld upon the day of operation. Just prior to operation, the animal was released from his cage and caught by a trained monkey handler From 0 8 to 1.8 ml of veterinary Nembutal was administered intraperitoneally. Within a few minutes the animals were quiet enough to permit shaving and positioning upon the operating table. These small doses of barbiturate were seldom adequate for surgical anesthesia, and reinforcement with open drop ether some time during the course of the operation was generally required Postoperatively the animals were wrapped in a cotton blanket, and they recovered from anesthesia within thirty minutes to several hours

Sudden and Complete Occlusion of the Portal Vein

The peritoneal cavity was generally entered through a right upper rectus muscle-splitting incision. After incising the peritoneum of the hepatoduodenal ligament, the portal vein was readily dissected free. In a few of the early experiments this was merely doubly ligated, however, in the majority it was divided between two ligatures as near the hilum of the liver as possible. Following division, the two ends of the portal vein retracted, leaving a gap of from 0.5 to 1.5 cm depending upon the size of the animal In a few monkeys a segment of vein about 1 cm. in length was excised. Immediately after occlusion the spleen became tense, and all of the veins on the greater and lesser curvature of the stomach, in the mesentery of the small bowel, and of the right colon became intensely congested On occasion, this was observed over a period of an hour or so before closure of the abdomen. During this period the picture did not change. The abdominal incisions were closed in layers with interrupted or continuous sutures of fine silk

Results

A total of 76 monkeys were subjected to sudden and complete occlusion of the portal vein by this method Sixty-seven of these were [illegible]

teen animals died within a few hours to several days after operation In 6 an obvious cause of death could not be found At autopsy all that could be detected was marked congestion of the abdominal

terial pressure changes in 6 monkeys is reproduced in Figure 114. This is in sharp contrast to the dog, in which the systemic arterial pressure falls rapidly to low levels and death occurs



Fig 117 Macaca mulatta monkey Portal venogram obtained immediately after portal occlusion This monkey survived quite uneventfully (From Child et al Ann Surg, vol 132, 1950)

within thirty minutes to two or three hours The tracing of a typical canine experiment is reproduced in Figure 115.

2 PORTAL VENOUS PRESSURE. Changes in portal venous pressure induced by portal occlusion have been studied in animals This rises promptly from 8 to 10 cm of saline to 30 to 60 cm of saline where it remains for several hours It then begins to fall so that by the end of six to ten days it has returned to almost the pre-occlusion level These studies have been diagrammed in Figure 116 In 27 monkeys the portal pressure was measured at intervals of three, six, and nine months after portal occlusion In none of these animals was the portal pressure found elevated above normal Based upon these experiments, the conclusion has been reached that persistent portal hypertension cannot be produced in monkeys by occlusion of the portal vein at the

Fig 115 In the dog, sudden and complete occlusion of the portal vein results in a steady decline in systemic arterial blood pressure. Within thirty to 120 minutes or so, the dog dies having bled to death into his splanchnic venous bed

Macaca Mulatta Monkey - Changes in Portal Pressure Produced by Occlusion of the Portal Vein

Monkey No	A Before occl	B 10 min. after occl	C 6-10 days after occl
24	16	24	17
25	14	57	20
26	13	38	18
27	13	53	18
28	9	56	
29	9	50	
30	18	47	
32	12	40	15
31	9	58	16
33	8	50	
34	17	42	
35	10	57	17
37	11	46	12
40	13	50	14
41	9		14

Fig 116. Although marked elevations in portal pressure far above normal can be produced in the monkey by sudden occlusion of its portal vein, these are not sustained. Within six to ten days after occlusion of the portal vein, the portal pressure returns to nearly its preoccluded level.

from 20 to 50 ml. of 35 per cent Diodrast injected into a small vein in the upper jejunal mesentery. A roentgenogram was taken as the last few milliliters of contrast medium was being injected. *This has generally provided a very satisfactory method* of following the various changes taking place in splanchnic hemodynamics as the animals adjust themselves to doing without a portal vein



Fig 119 Macaca mulatta monkey Portal venogram four months after occlusion of the portal vein Here the portal pressure is normal, and the point of occlusion has been completely by-passed Practically the entire amount of the injected radio-opaque substance enters the liver directly Most of the collaterals visualized at the end of six weeks have disappeared (From Child et al Ann Surg, vol 132, 1950)

As a result of these studies, three general phases *in the re-*adaptation of splanchnic to portal occlusion can be described [illegible] sion From approximately one week to two months after portal occlusion, many collaterals appear in the neighborhood of the portal obstruction (Fig 118) Later, in from two to six months, the many collaterals seen earlier seem to coalesce and by the end of four to six months one or two large vessels completely by pass

hilum of the liver In 3 animals progressive occlusion of the portal vein has been produced by means of a cellophane band Portal hypertension was not produced by this method either

3 PORTAL VENOGRAPHY FOLLOWING PORTAL OCCLUSION. Early in these studies, an effort was made to assess the portal systemic



descending into the pelvis via the inferior mesenteric vein. This is then regathered in sufficient amounts to permit visualization of the iliacs, inferior vena cava, and spermatic vein In addition, a number of collaterals are forming which by-pass the point of obstruction and partially visualize the liver Portal pressure at this time was 13 cm of saline. (From Child et al: Ann Surg, vol 132, 1950)

communications grossly at autopsy and by means of various colored injection masses Both of these methods proved unsatisfactory for a number of reasons After death, the veins collapsed and it was impossible to follow their course accurately When injection masses were used, the question arose as to how many of the communications were normally in operation and how many had been artificially produced by the technique These efforts, therefore, were shortly abandoned and portal venography substituted. Approximately 30 animals were reoperated upon at various intervals after occlusion of the portal vein and

6 GROSS AND MICROSCOPIC HEPATIC MORPHOLOGY In over 25 monkeys the liver was inspected and biopsied at intervals of from one week to four weeks after operation In several instances biopsy material was studied as long as two years after portal occlusion Neither gross nor microscopic abnormalities were observed

the site of obstruction. The entire mass of contrast medium now enters the liver directly. It has seemed logical to conclude, therefore, that the reason portal hypertension does not persist is found in the enormous capacity of this animal to open up existing collateral circulatory beds and to establish new ones of considerable magnitude (Figs. 119, 120).



Fig 120 [illegible]
of the port[illegible]
animal to b[illegible]
(From Child et al Radiology, vol 57, 1951)

4 ASCITES AND SPLENOMEGALY In none of these animals could persistent ascites or enlargement of the spleen be produced. Rarely it was thought that ascites might be present for perhaps a few days after operation, but certainly, if indeed it was present at all, it disappeared within a week or less

5 LIVER FUNCTION Pre-occlusive and post-occlusive liver function was studied in 12 animals by means of the following tests [illegible]

[illegible]

time, and [illegible] Postoperative [illegible] generally performed upon the first, the third, the seventh, the thirteenth, and the twentieth days after operation These tests failed to reveal evidence of depression of liver function

had been attempted in one stage Four animals survived ten, seventeen, twenty-seven, and forty-eight days after operation before succumbing to one or another postoperative complication These deaths, however, were clearly not due to resection The majority of the animals died because of postoperative complications which could have been avoided had it been possible to administer any semblance of modern postoperative care Almost literally the animals were on their own from the first day after operation on Gastric suction was



Fig 121 Specimen removed from monkey #66 who successfully underwent two-stage resection of the lower third of the stomach, the head and body of the pancreas together with the portal vein and segments of the splenic, superior, mesenteric, and inferior mesenteric veins (From Child et al Ann Surg, vol 132, 1950)

out of the question The tubes placed in the animal's stomach at the time of operation were always removed within the first twenty four postoperative hours An infusion or transfusion required a general anesthesia, and two agile men were required to give a monkey one injection of penicillin A summary of the protocols of these 23 animals is recorded in Table 17

Macaca mulatta monkey No 66 survived forty-eight days and then succumbed in anuria two days after portal venography had been performed with 40 ml of 70 per cent Diodrast During his period of survival, however, he ate well, gained in weight, and failed to manifest any evidence of impaired liver function A portal venogram obtained in this animal forty six days after operation is reproduced in Figure 122 This is of particular interest for the extensive collaterals developing in the pancreaticoduodenal bed which were capable within forty-six days of conducting practically all of the injected

APPENDIX 2

Pancreaticoduodenectomy with Resection of the Portal Vein in the Macaca Mulatta Monkey

AFTER demonstrating that the monkey survived sudden and complete portal occlusion, it was postulated that perhaps this animal would tolerate a block resection of the head of the pancreas, the duodenum, and the portal and superior mesenteric veins. This was attempted in 6 animals with complete failure of all six experiments The monkeys died in shock during the course of the procedure or shortly thereafter due to blood loss from the field of operation As

[illegible]

occurred It was concluded, therefore, that a successful one-stage operation was out of the question.

In view of the observation that the severe portal hypertension produced by sudden portal occlusion subsided to near normal levels within seven to fourteen days, a two-stage operation was designed which proposed to make use of [illegible] stage the portal vein was simply li[illegible] was reopened and the lower end of the stomach, the head [illegible] pancreas, the entire duodenum, and the upper few centimeters of the jejunum were resected together with the portal and superior mesenteric veins *In Figure 121 is reproduced a photograph of a* specimen so removed. This demonstrates the extent of the resection; the portal vein is clearly shown.

Such a two-stage operation as this has been performed in 23 monkeys. The postoperative mortality was high, and the survival periods

[illegible]

in normal portal circulatory dynamics occasioned by resection of the portal, splenic, and superior mesenteric veins. The bleeding at the operating table was not so excessive as it had been when resection

12	66	10-27-50	11-10-50	14	150	Penicillin and streptomycin	48 days	Anuria 2 days after portal venogram (40 ml 70% Diodrast)
13	68	11-17-50	12-15-50	29	150	None	1 hour	Ligation of hepatic artery
14	73	12-1-50	12-28-50	27	150	None	12 hours	Shock (external blood loss)
15	78	12-8-50	12-25-50	17	300	Penicillin and streptomycin	17 days	Cholangiohepatitis (stricture choledochojejunostomy)
16	79	12-15-50	12-24-50	9	300	None	3 hours	Not determined
17	82	1-26-51	2-18-51	23	400	None	1 hour	Marked mesenteric lymphadenitis †
18	87	12-28-50	1-12-51	15	300	None	12 hours	Dehiscence common duct and pancreatic anastomosis Acute chemical peritonitis
19	88	12-29-50	1-8-51	10	300	Penicillin and streptomycin	24 hours	Gangrene entire jejunum
20	95	2-2-51	2-23-51	21	300	Penicillin and streptomycin	36 hours	Dehiscence common duct anastomosis Acute biliary peritonitis
21	124	5-18-51	5-25-51	7	110	None	1 hour	Shock (external blood loss)
22	126	6-1-51	6-8-51	7	375	None	14 hours	Acute gastric dilatation
21	129	6-15-51	6-29-51	14	350	None	18 hours	Acute anasarca (excessive i.v. fluids)

* Animals 25-95, portal vein divided at 1st stage Animals 124-129 superior mesenteric vein divided at 1st stage
† This animal died during an epidemic of acute mesenteric lymphadenitis in animal colony (cause undetermined)
From Child et al Ann Surg *132* 475-495, 1950

TABLE 17

MACACA MULATTA MONKEY TWO STAGE PANCREATICODUODENECTOMY WITH RESECTION OF THE PORTAL VEIN

EXP. NO	MONKEY NO *	DATE OF		INTERVAL (DAYS)	BLOOD TRANSFUSION ml	ANTIBIOTICS	POSTOP SURVIVAL	CAUSE OF DEATH
		1st stage	2nd stage					
1	25	11-9-49	11-15-49	6	None	None	39 hours	Acute gastric dilatation Aspiration of vomitus
2	26	11-2-49	11-4-49	2	None	None	12 hours	Ligation of sup mesenteric and hepatic arteries
3	27	11-16-49	11-22-49	6	None	None	5 hours	Shock (external blood loss)
4	24	11-6-49	11-14-49	8	None	None	5 hours	Shock (external blood loss)
5	31	12-7-49	12-15-49	8	None	None	5 hours	Not determined
6	37	1-31-50	2-15-50	12	150	Penicillin	48 hours	Acute gastric dilatation
7	41	2-16-50	2-23-50	7	None	Penicillin	10 days	Pneumonia Wound infection and dehiscence
8	40	2-23-50	3-7-50	12	70	None	4 hours	Shock (external blood loss)
9	64	9-29-50	10-5-50	6	150	Penicillin	27 days	Perforated gastrojejunal ulcer Multiple liver abscesses
10	63	10-6-50	10-14-50	8	150	Penicillin and streptomycin	12 hours	Shock (external blood loss)
11	65	10-20-50	10-31-50	11	150	None	On table	Hemorrhage from superior mesenteric artery

APPENDIX 3

Resection of the Hepatic Artery in the Macaca Mulatta Monkey

HAVING discovered that the Macaca mulatta monkey survives abrupt ligature of the portal vein, it seemed appropriate to investigate the effects of hepatic arterial ligation in this animal. Interest in these experiments coincided with Markowitz's demonstration that the dog survives hepatic dearterialization provided this animal is protected with adequate doses of penicillin.

Nineteen adult monkeys were selected for this study, and their entire extrahepatic arterial systems were excised from the origin of the hepatic artery on the celiac axis through the various points of entrance of this vessel's branches into the liver. Figure 123 outlines the extent of this resection. Of the 19 animals operated upon, one died two hours after resection. It was not believed that death was due to removal of the hepatic artery. All the remaining animals survived apparently undisturbed by the procedure. Five animals received penicillin and/or dihydrostreptomycin for from one to five days postoperatively; the other 13 animals did not receive any form of chemotherapy.

Liver function was studied both preoperatively and postoperatively by means of the following liver function tests: cephalin flocculation, prothrombin time, total serum protein and albumin globulin ratio, hippuric acid clearance, and Bromsulphalein retention. These determinations were made at intervals of from ten months to 125 days after operation. The only test which showed any evidence of abnormality was the cephalin flocculation. Here a one to two plus reaction was encountered in 10 of the 18 animals. This minor variation from the normal could not be correlated either with the clinical course of the animals or with postmortem examination of their livers.

Liver biopsies or autopsies were performed upon all these animals in from two hours to twenty-eight days after complete resection of the hepatic artery. The results can best be studied by dividing the

contrast medium directly to the liver. At the time of portal venography the portal pressure was 21 cm. of saline. Although this is about 10 cm above normal, it cannot be classified as portal hypertension comparable with that seen in man in extrahepatic portal



Fig 122. Monkey #66 This venogram was taken forty-six days after resection of the portal vein, duodenum, and head of the pancreas The three arrows point toward the extensive collaterals which have formed within this short period of time between the portal circulation and the liver. This animal ever manifests a remarkable ability to return blood to his liver. (From Child et al: Surg, Gynec, & Obst, vol 94, 1952.)

block due to thrombosis of the portal vein. It is more than probable

section of the portal vein performed in man and described in Chapter 15 was based

APPENDIX 3

Resection of the Hepatic Artery in the Macaca Mulatta Monkey

HAVING discovered that the Macaca mulatta monkey survives abrupt ligature of the portal vein, it seemed appropriate to investigate the effects of hepatic arterial ligation in this animal. Interest in these experiments coincided with Markowitz's demonstration that the dog survives hepatic dearterialization provided this animal is protected with adequate doses of penicillin.

Nineteen adult monkeys were selected for this study, and their entire extrahepatic arterial systems were excised from the origin of the hepatic artery on the celiac axis through the various points of entrance of this vessel's branches into the liver. Figure 123 outlines the extent of this resection. Of the 19 animals operated upon, one died two hours after resection. It was not believed that death was due to removal of the hepatic artery. All the remaining animals survived apparently undisturbed by the procedure. Five animals received penicillin and/or dihydrostreptomycin for from one to five days postoperatively, the other 13 animals did not receive any form of chemotherapy.

Liver function was studied both preoperatively and postoperatively by means of the following liver function tests: cephalin flocculation, prothrombin time, total serum protein and albumin-globulin ratio, hippuric acid clearance, and Bromsulphalein retention. These determinations were made at intervals of from ten months to 125 days after operation. The only test which showed any evidence of abnormality was the cephalin flocculation. Here a one to two plus reaction was encountered in 10 of the 18 animals. This minor variation from the normal could not be correlated either with the clinical course of the animals or with postmortem examination of their livers.

Liver biopsies or autopsies were performed upon all these animals in from two hours to twenty-eight days after complete resection of the hepatic artery. The results can best be studied by dividing the

animals into two groups: those receiving antibiotics and those in whom chemotherapy was not employed. The livers of all 5 animals who received penicillin and/or dihydrostreptomycin were entirely normal. Infarcts could not be found nor was there evidence of acute cholecystitis.

Of the 13 untreated animals, the livers of 8 were completely normal, but the gallbladders in 5 were shrunken and fibrotic. In

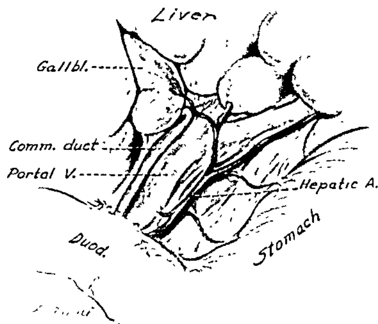


Fig. 123. Hepatic arterial branches in the Macaca mulatta monkey. All the branches here represented were resected in dearterialization of the liver of this animal.

3, the gallbladders were normal. In the livers of 5, however, were demonstrated multiple areas of infarction which ranged in size from 2 mm. to 10 cm. in diameter. In one animal, autopsied three weeks

bladder which had been completely walled off with omentum. Scattered

ous small

meters to

throughout the three weeks he was permitted to survive his oper-

ation All of his liver function tests were normal The infarcts found in the livers of the remaining 4 animals presented a highly irregular pattern In 2 there were perhaps a dozen or more, while in 2 there were upwards of a hundred tiny areas of necrosis In 3 of these animals the gallbladders were gangrenous Microscopic sections of the infarcted areas were made and revealed varying degrees of healing, the site of early infarcts presented as necrotic foci, while those of longer duration appeared under the microscope as fibrotic scars

In view of the regularity with which these animals survived hepatic dearterialization, it was considered imperative that every effort be made to determine whether or not arterial collaterals existed Several different tests were employed Immediately following division of the hepatic artery at the celiac axis, 35 per cent Diodrast was injected liverwards The liver was completely visualized on x-ray film in all of the experiments This was accepted as evidence that the liver received at least its major arterial blood supply from the hepatic artery In several animals either the right or left main hepatic arteries were occluded Under these circumstances, the lobes normally supplied by the occluded vessel could not be visualized These experiments indicated that interlobar arterial anastomoses do not exist in the primate

The abdominal aorta just cephaled to the origin of the celiac axis was occluded in several animals Thirty-five per cent Diodrast was then injected in large amounts into the thoracic aorta In none of these animals could collaterals to the liver be demonstrated Another experiment consisted of the injection of India ink into the thoracic aorta In normal animals the liver became black immediately, but in those in whom the hepatic arterial tree had been resected, the discoloration of the liver was much delayed, appearing only after the ink had had time to traverse the mesenteric capillary bed and enter the liver by way of the portal vein In 2 animals the portal vein was occluded and the hepatic arterial tree resected In these the ink reached the liver after ten to fifteen minutes, but the routes were never identified

The livers have been cultured in over 30 normal monkeys, and this organ proved sterile both aerobically and anaerobically This may, of course, explain why the monkey survives, whereas the dog, from the liver of which Bacillus welchii can regularly be recovered, dies after hepatic dearterialization The conclusion which can be drawn from these experiments is that 13 Macaca mulatta monkeys have survived hepatic dearterialization without protection by antibiotics

APPENDIX 4

Sudden and Complete Occlusion of the Hepatic Veins in the Macaca Mulatta Monkey

AFTER proving that the Macaca mulatta monkey survives sudden and complete occlusion of its portal vein, it became a matter of interest to determine whether this animal could tolerate similar occlusion of its hepatic veins Preliminary examination of the hepatic veins of the monkey promptly demonstrated that these vessels were many and entered the vena cava over a broad saddle-shaped area well imbedded within the inferior border of the liver. One or two experiments upon living animals demonstrated conclusively that it was virtually impossible to occlude all of the vessels simultaneously The liver tore and bled sufficiently to precipitate these animals into

by such profuse hemorrhage from the cut surfaces of the liver that the animals died before occlusion of all the hepatic veins could be completed In considering other techniques, the only one of promise consisted in occlusion of the vena cava above the entrance of the hepatic veins This, however, did not prove an attractive experiment, for its results could not be considered unequivocally related to hepatic venous occlusion alone

Attention was then turned to the development of a method whereby the hepatic veins could be suddenly occluded and at the same time normal caval flow preserved. A reasonably satisfactory technique was worked out by inserting a polyethylene tube of large diameter into the vena cava in such a position that it straddled the entrance of the hepatic veins With this prosthesis in place, two ligatures were tied tightly about the cava just above and just below the hepatic veins With the animals well heparinized, a few

tal experiments convinced us that here was a practical method for suddenly and completely occluding the hepatic veins

Fourteen Macaca mulatta monkeys were subjected to occlusion of the hepatic venous drainage in this fashion, and the following observations recorded

1 SURVIVAL TIME After complete occlusion of the hepatic veins, the average survival time was thirty five minutes A few of the animals died precipitously in ten minutes, while the longest postoperative period of life was sixty minutes In 7 animals, isotonic saline was administered throughout the course of the experiment at a mean rate of 100 ml an hour This prolonged the average survival time approximately eighteen minutes Two animals received 90 ml of citrated monkey blood during the course of the experiment, one survived twenty-five minutes, the other three and one-half hours

2 PORTAL PRESSURE In 10 animals portal pressure was measured before, during, and after hepatic venous occlusion This rose from a pre occlusive level of from 7 to 8 cm of saline to an average of 35 Shortly after reaching its highest level, portal pressure fell progressively, reaching its pre-occlusive level at the time of death of the animal

3 SYSTEMIC ARTERIAL PRESSURE Immediately after occlusion of the hepatic veins, the systemic arterial pressure as measured in the femoral artery fell precipitously from the normal level of 110 to 120 mm of mercury to 20 to 30 mm of mercury Here it remained until the animal expired

4 HEMATOCRIT AND SERUM PROTEIN Immediately after occlusion of venous drainage of the liver, a steady fall in the hematocrit in the peripheral venous blood was observed This averaged 12 8 per cent in approximately thirty minutes In one animal the hematocrit fell from 38 7 to 9 4 within thirty-four minutes In 3 animals serum protein levels were determined serially, the albumin and globulin dropped an average of 2 5 grams per 100 ml and 1 7 grams per 100 ml respectively

5 GROSS AND MICROSCOPIC EXAMINATION OF THE LIVER The livers of all of these animals were examined immediately after death Their weight was found increased an average of 20 per cent over the normal They were tense and a dark blue in color In each instance the pancreas and small bowel mesentery were edematous There was no detectable change in the size of the spleen Examination of microscopic sections of the liver revealed that the central veins and adjacent sinusoids were hugely dilated by packed red cells

These experiments were conducted primarily to investigate whether the clinical syndrome of hepatic venous occlusion in man could be reproduced in the experimental animal Obviously this

objective was not accomplished The prolonged survival periods described in patients manifesting this disease must depend upon slow progressive occlusion of these vessels. Although blood volume studies were not performed upon these animals during the course of the experiments, circumstantial evidence indicates that death was due to depletion of the effective circulating blood volume into the portal and hepatic venous beds. The profound drop in red cells which occurred seemed to indicate that the liver was able to trap huge numbers of red cells and at the same time to release serum into the portal venous system by returning it to the systemic system by way of the hepatic lymphatics.

The Effect of Epinephrine upon the Portal Venous Pressure of Normal Dogs, Normal Monkeys, Normal Men, and of Patients with Moderate and Advanced Cirrhosis

FROM time to time in the past, innumerable investigations have been made of the effect of epinephrine upon portal venous pressure. Most of these studies, however, have been performed upon a number of different experimental animals (see Chapter 7). Because the portal system in man is generally unavailable for experimentation, very little is known of how it would react to this hormone. The following series of experiments have been performed in the laboratories of surgical research and in the operating rooms of the New York Hospital. In general, they were planned to confirm some of the older observations obtained in the dog and to extend these observations to patients with normal as well as abnormal livers.

Methods

A standard method for making these observations was employed. This consisted of inserting a polyethylene catheter into the superior mesenteric vein. In animals, variations in portal pressure were detected by means of an electromanometer and recorded appropriately. Clotting in the cannulas was prevented by small amounts of heparin. In man, a spinal manometer filled with saline was attached to the cannula and pressure changes recorded by direct observation. A continuous record of systemic arterial pressure was kept as a control observation on the effectiveness of the hormone injected. All injections of epinephrine were made directly into a small venous radicle in the upper jejunum.

Normal Dogs

In over 20 experiments, the portal pressure rose precipitously immediately after injection of 0 1 to 0.5 ml of 1:1000 epinephrine This observation, made many times in the past by innumerable investigators, does not warrant detailed comment here. Attention should, however, be called to the fact that the rise in portal pressure

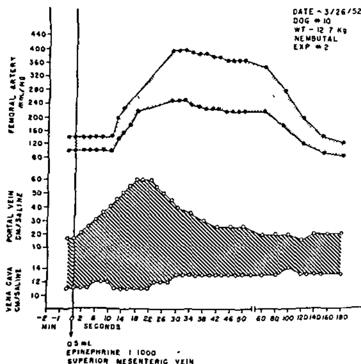


Fig 124. Effect of epinephrine upon the portal pressure of a dog with a normal liver The marked rise produced contrasts sharply with the moderate rise characteristic of the monkey and man (See Figure 52, page 102.)

is far above that obtained in either normal man or monkey. A typical curve for the dog is reproduced in Figure 124

Normal Monkeys

The effect of 0 1 to 0 5 ml of 1:1000 epinephrine was observed in a consecutive series of 9 Macaca mulatta monkeys. In each instance, the portal pressure rose promptly and then returned to normal within ten to twenty minutes The levels reached, however, were far lower than those observed in the dog A typical curve for this animal is reproduced in Figure 125

Normal Man

The effect of the injection of 0 5 ml of 1 1000 epinephrine was observed in 3 patients whose livers were normal These observations were made just prior to cholecystectomy for chronic cholecystitis and cholelithiasis and to gastrectomy for chronic duodenal ulcer In each instance, the portal pressure rose a few centimeters of saline

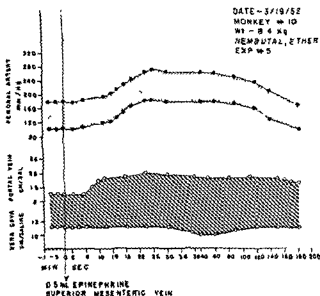


Fig 125 Reaction of portal pressure to epinephrine in the normal monkey Here a small dose of epinephrine produces a modest rise in portal pressure This is nowhere near as great as in the dog, the curve obtained corresponds closely to that encountered in normal man Neither in this animal nor in the dog is the inferior caval pressure materially affected

These degrees of elevation were comparable with those obtained in the monkeys rather than with those seen in the dogs A representative curve is reproduced in Figure 126

Abnormal Man

The effect of injection of the *same amount of epinephrine* was studied in 3 patients whose livers were abnormal but not the site of typical Laennec's cirrhosis In one patient the common bile duct was obstructed due to a malignant tumor of the head of the pancreas The portal pressure was normal and the response to epinephrine was normal, namely a moderate rise in portal pressure

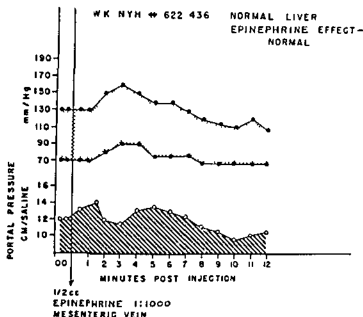
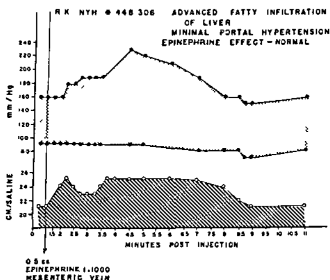


Fig 126 Effect of epinephrine upon portal pressure of normal man Here the characteristic curve obtained is a moderate initial elevation followed by a slight drop and a secondary rise



In the second patient the liver was the site of an early biliary cirrhosis due to obstruction of the common hepatic duct by a malignant tumor. This had also partially obstructed the portal vein just within the porta hepatis and produced a portal hypertension of 29 cm. of saline (see Fig. 95, page 280). Here 0.5 ml. of 1:1000 epinephrine resulted in an expected modest rise in portal pressure. This curve is reproduced in Figure 128.

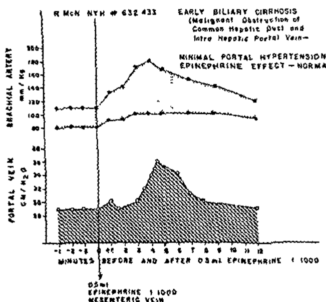


Fig. 128. Effect of epinephrine upon the portal pressure of a patient with early biliary cirrhosis and minimal portal hypertension due to partial intrahepatic obstruction of the portal vein. The expected rise appears intensified.

In the third patient the liver was diffusely infiltrated with fat and the portal pressure was moderately elevated (21 cm. of saline). Epinephrine produced the expected rise. This curve is reproduced in Figure 127.

The effects of 0.5 ml. of epinephrine were studied in 2 patients with minimal to moderate portal cirrhosis and in 5 patients with advanced cirrhosis. In all 7, clinically important degrees of portal hypertension were present, and these subjects all had had severe hematemeses from esophagogastric varices. The observations were made just prior to decompression of the portal venous system by means of a portacaval shunt. In the 2 patients with moderate cirrhosis, the portal pressure rose to the same levels encountered in patients and monkeys with normal livers. In the 5 patients with advanced cirrhosis, the portal pressure fell sharply. This apparent reversal of the epinephrine

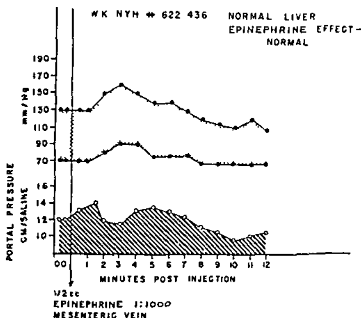
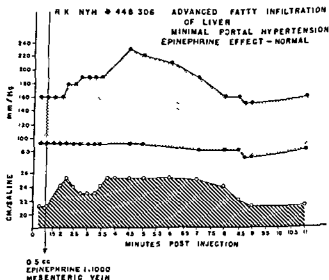


Fig 126 Effect of epinephrine upon portal pressure of normal man Here the characteristic curve obtained is a moderate initial elevation followed by a slight drop and a secondary rise.



effect in advanced cirrhosis has been commented upon elsewhere page 94). In Figures 129 and 130 are reproduced the curves of two patients with minimal to moderate cirrhosis in whom the response to adrenalin was normal In Figure 131, A, B, C, and D are reproduced the curves of 4 patients with advanced cirrhosis whose epinephrine curves were reversed

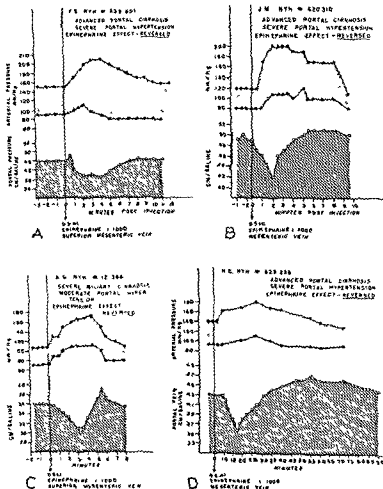


Fig 131 Reversal of normal epinephrine effect in patients with advanced *cirrhosis and portal hypertension. On analyzing these curves, the conspicuous* feature is a reversal of the initial rise In each instance the secondary rise to slightly above *the pre-injection pressure* is evident (*See* Cases #23, p 362 #17 p 364, and #18, p 365)

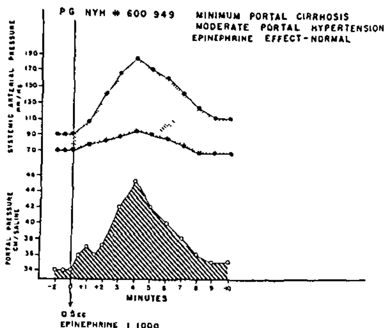


Fig 129 P.G. N.Y.H. #600949 Although moderate portal hypertension and cirrhosis were both present, the expected rise was obtained. The typical dicrotic curve, although present, is not as clear cut as in Figure 130.

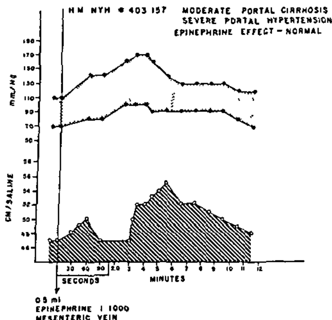


Fig. 130 Effect of epinephrine upon the portal pressure of a patient with portal hypertension due to moderately advanced cirrhosis Although the portal pressure is high, the primary rise, the transient fall, and the secondary rise characteristic of normal man are evident. (See Case #19, p 366.)

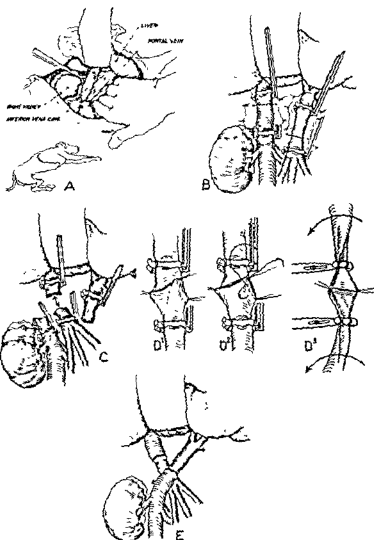


Fig 132 These figures, which are largely self-explanatory, demonstrate the various stages in transpositioning the portal and caval circulations During the brief period of complete obstruction to both circulations, it is important that a transfusion be kept running briskly Before transfusion became part of the procedure, several dogs died in profound shock

APPENDIX 6

Hepatic Regeneration in Dogs with Transposition of the Portal and Caval Circulations

HEPATIC regeneration following a 70 per cent hepatectomy has been studied in 15 dogs. 8 with portacaval transposition (Fig. 132), 6 with normal hepatic circulation, and 1 with an Eck fistula (end-to-side portacaval shunt)

TABLE 18

AREA OF SHADOW CAST BY RIGHT LOBE OF LIVER ON CONSECUTIVE VENOGRAMS BEFORE AND AFTER PARTIAL HEPATECTOMY IN DOGS WITH PORTACAVAL TRANSPOSITION

DOG NUMBER	AREAS IN PLANIMETER UNITS			
	BEFORE PARTIAL HEPATECTOMY	AFTER PARTIAL HEPATECTOMY		
		1 Week	4 Weeks	6 Weeks
738	265	369	516	570
737	213	310	372	397
741	202	456	474	508
746	217	214	333	
756	381	795	692	
760	335	598	664	

Hepatic venograms, obtained by injecting contrast material directly into the inferior vena cava, were made before and after partial hepatectomy in order to follow hepatic regeneration in vivo in the dogs with portacaval transposition When the hepatograms made prior to partial hepatectomy were compared with those taken at intervals afterward, it was clear that there was a great increase in the area and density of liver filled with contrast material (see Fig 57, A through E, p 144) These areas were measured with a planimeter

B Normal Hepatic Circulation								
769	11 4	279	120	10 4	285	165	42	59
770	12 3	348	147	12 9	322	185	57	53
797	13 9	208	89	15 0	337	238	30	114
829	19 3	255	109	17 3	318	209	43	82
830	22 7	325	140	21 8	451	311	43	96
831	17 2	329	141	15 9	288	147	42	45
Average Regeneration 75 per cent ± S D 37								
C Eck Fistula								
772	16 1	421	181	10 7	174	−7	29	0

TABLE 19

HEPATIC REGENERATION FOLLOWING PARTIAL HEPATECTOMY IN DOGS WITH

A PORTACAVAL TRANSPOSITION
B NORMAL HEPATIC CIRCULATION
C ECK FISTULA

A Portacaval Transposition

DOG NUMBER	WEIGHT OF DOG AT PART HEPATECT. Kg	WEIGHT OF LIVER REMOVED Gm	ESTIM WEIGHT OF HEP REMNANT Gm	WEIGHT OF DOG AT AUTOPSY Kg	WEIGHT OF LIVER AT AUTOPSY Gm	ESTIM GAIN IN LIVER WEIGHT Gm	INTERVAL BETWEEN OP AND AUTOPSY Days	LIVER REGENERATION Per cent
729	15.5	273	117	13.6	302	185	38	68
736	16.1	302	130	15.2	371	241	36	80
738	13.6	335	143	12.3	230	87	60	25
737	10.8	251	108	9.3	159	51	50	20
741	11.1	201	81	9.6	177	96	50	49
746	10.2	159	68	9.3	161	93	45	59
756	21.5	322	138	18.2	320	182	45	57
760	15.4	272	117	14.3	230	113	35	42

Average Regeneration 50 per cent ± S D 21

APPENDIX 7

Portal Hypertension—Case Abstracts

(See also Figures 77 A and B)

PORTACAVAL SHUNTS

Case #0 P G N Y H #407,085 Male Aged 49 years

Cirrhosis of the Liver, Portal Hypertension, Diabetes, Esophageal Varices, and Hematemesis

P G, a heavy drinker for many years, had been known to have *cirrhosis of the liver for about sixteen months prior to admission* The night before his first admission to this hospital he passed a large tarry stool, and several hours later he vomited a copious amount of blood After admission, he continued to vomit blood This w...

...ces wer...

discharged to return at a later ...

later he bled again and was admitted for portal decompression

wa...

en...

weeks, *P G was discharged Just before discharge, patency of* the shunt was demonstrated by transcardiac catheterization

P G was readmitted to the hospital several times over the next three years in impending hepatic coma. On supportive treatment he improved each time and was discharged

Three years after portal decompression he died in another hospital

Case #1 J M N Y H #578,933 Male Aged 26 years

Cirrhosis of the Liver (Schistosomiasis), Portal Hypertension, Esophageal Varices, and Hematemesis

J M, a twenty six year old Puerto Rican man, was well as far as he knew until three years *prior to admission*, at which time

ankles and abdomen ...

pear following his next hematemesis

[illegible] They are viewed as striking

[illegible] regeneration was calculated as follows. The weight of the liver resected was multiplied by 3/7 to obtain an estimate of the weight of the hepatic remnant. The factor 3/7 was derived from the results of dissection of normal livers in which the weight of the liver resected was found to amount to 71 per cent of the total weight of the liver (+ or − Standard Deviation 4). The weight of the hepatic remnant was subtracted from the weight of the liver removed at autopsy in order to arrive at a figure for the gain in weight, in grams, of the hepatic remnant during the experimental period. The gain was divided by the weight of liver resected and multiplied by 100 to express regeneration in per cent. Thus, if gain equaled weight resected, then regeneration would be 100 per cent.

By this method of calculation, it was found that the dogs with portacaval transposition replaced 50 per cent of the weight of liver resected, those with normal hepatic circulation 75 per cent; and the dog with an Eck fistula none at all (see Table 19 and Fig. 57 F, p. 144).

The evidence, then, supporting the contention that hepatic regeneration occurred in the dogs with portacaval transposition is derived from two independent sources: the venograms and calculations of percent regeneration based upon liver weight. Comparison with the dog with an Eck fistula clearly establishes that regeneration can occur in the absence of portal blood provided that systemic venous blood is substituted.

The relative efficacy of systemic venous blood versus portal blood [illegible]

[illegible] was not possible to prove they could not have been drawn from one and the same population. Yet the magnitude of the difference between the two means and the proximity of the results of the tests of significance (e.g., t equals 1.98) to the critical value (where t must equal 2.18 or more) are such as to suggest that a real as well as apparent difference exists between the two groups. The inference, then, is that systemic venous blood is almost, but not quite, as effective in supporting liver regeneration as portal blood. The essential factor in liver regeneration appears, therefore, to be the volume of blood delivered to the liver rather than its source.

other hospital where an ulcer on the lesser curvature was found, and the patient explored At operation the vessels of the coronary

Hospital for

procrastinated until another hemorrhage precipitated his admission to *The New York Hospital J R 's past history included* the ingestion of large amounts of whiskey over the years and one episode of jaundice which subsided after he stopped his alcoholic intake

PHYSICAL EXAMINATION On admission J R was in apparent

ity *Esophageal varices were demonstrated on x rays of the esophagus*

OPERATION Two weeks after admission an end to side portacaval shunt was performed When the shunt was opened, the pressure fell from 36 to 24 cm of saline

POSTOPERA
developed p
teses Slowly
that the shu

Case #4 D K N Y H #582,973 Female Aged 38 years

Cirrhosis of the Liver, Esophageal Varices, and Esophagogastric Bleeding

D K , a hard working alcoholic business woman, had been well until about nine months to a year prior to admission At this time she developed amenorrhea and seemed to become unduly *fatigued For several months prior to admission she* vomited small amounts of blood daily and lost weight steadily On ad-

erythematous

really been well She has not, however, vomited blood during this period (See note, p 379)

On admission, J.M. appeared chronically ill and malnourished. Both his liver and spleen were readily palpable, abdominal fluid was present, and ova of Schistosoma mansoni were found in his stools. Large varices of his esophagus were demonstrated by x ray

An end-to-side portacaval shunt was satisfactorily fashioned This reduced his portal pressure from 32 to 22 cm. of saline His postoperative course was marred by the formation of large amounts of ascitic fluid This subsided, however, and he was discharged five weeks after operation J.M. was followed regularly for three months after operation. During this period, he was well and did not bleed. He then returned to Puerto Rico and has not been heard from since.

Case #2 D M N.Y H. #466,182 Male Aged 46 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Hematemesis

D M was first told that he had an enlarged liver some nine years before he was admitted to the hospital because of hematemesis Of possible significance was the fact that he had received carbon tetrachloride in treatment for a Taenia saginata infestation. Three years before admission he began to fatigue

[illegible]

[illegible] prior to admission

Physically, D M was in good condition. An esophagogram revealed extensive varices and an end to-side portacaval shunt reduced his portal pressure from 35 to 11 5 cm of saline. Although postoperatively D M. gained in strength slowly, he finally left the hospital in reasonably good health three weeks after operation. He has been followed closely for two and one-half years During this time, his varices have disappeared and, though he has not bled, he has never really enjoyed robust health (See note, p 379)

Case #3 J R. N Y.H #582,110 Male Aged 46 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Massive Hematemesis

HISTORY This forty-six-year-old white man was admitted to this hospital in his fourth episode of hemorrhage. The first had occurred a year before admission at which time a diagnosis of cirrhosis and esophageal varices had been made at another hospital Six months before admission he was admitted to yet an-

many large varices were demonstrated Thirteen days after admission, an end-to-side portacaval shunt succeeded in lowering her portal pressure from 42 to 27 cm of saline. (Portal venogram in Fig 93, p 278) Two weeks after operation she was discharged well She has been followed for two years, and on each visit has manifested excellent health Her spleen can no longer be palpated, and her varices have disappeared

Case #7 E D N Y H #531,465 Female Aged 40 years

Biliary Cirrhosis, Portal Hypertension, Esophageal Varices, and Hematemesis

mal and did not recur until two weeks prior to admission when

This lowered her portal pressure from 46 to 26 cm of saline Her postoperative course was uneventful and she was discharged on her sixteenth day after operation

She remained well for one year when an acute attack of small intestinal obstruction required a celiotomy for release of adhesions At this time her portal pressure was 17 cm of saline Two years after her shunt she is well save for an active duodenal ulcer

Case #8 R K. N Y H #596,344 Male Aged 45 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Hematemesis

For fifteen years prior to admission R K had regularly consumed numerous shots of whiskey daily This was apparently well tolerated Two days prior to admission he vomited a moderate amount of old blood and passed several tarry stools On admission to the hospital, R K appeared chronically ill. His liver was enlarged, and his skin mildly icteric Although varices were not demonstrated by x ray, R K's history favored esophageal varices with hemorrhage so strongly that a portacaval shunt, end to side, was performed This lowered his portal pres-

tions of hepatic failure cleared rapidly, and he was discharged eleven days after operation Since discharge, he has remained well (two years) and has worked regularly

Case #5 G G. N.Y H. #557,048 Male Aged 53 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices and Massive Hematemesis, Postoperative Serum Hepatitis

HISTORY G G., a fifty-three-year-old Iranian physician, presented himself at this hospital with a long history of hematemesis and tarry stools The first of these episodes occurred twelve years before admission and they were repeated almost annually. One year prior to admission esophageal varices were demonstrated and he developed sufficient ascites to require paracentesis. He was known, therefore, for a year prior to admission to have [illegible]

G G became lethargic and confused One effort to remove the balloon was followed by a brisk hematemesis of 700 ml, and the patient became comatose.

OPERATION As an emergency measure, the patient was taken to the operating room where an end-to-side portacaval shunt was performed This lowered his portal pressure from 45 to 21 cm. of saline

POSTOPERATIVE COURSE For several days bleeding continued, and G G was in desperate straits He received 8500 ml. of citrated blood and slowly recovered Nineteen days after operation he was discharged only to be admitted three and one-half months later with deepening jaundice, ascites, and edema of his legs After two months in the hospital, he recovered sufficiently and was discharged One year and three months after operation G G died at another hospital. At postmortem examination the shunt was found to be widely patent. Although this man did not bleed after operation, he was certainly never really free of hepatic decompensation at any time after his discharge from the hospital.

Case #6 S L N Y H #589,381 Female Aged 47 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Hematemesis

For approximately ten years prior to admission, S.L. had daily consumed generous amounts of sherry Two years prior to admission she had her first hemorrhage, and a diagnosis of cirrhosis was made Several days prior to admission she vomited blood again and passed several tarry stools She was found to be severely anemic and was admitted to the hospital.

Physical examination revealed several spider angiomas over her upper chest and an enlarged liver and spleen. Her spleen was just palpable below her left costal margin On esophagography

operated upon eight weeks after admission. A rapidly and easily performed end to side portacaval shunt reduced her portal pressure from 40 to 15 cm of saline

For three days after operation, M A did well She then suddenly passed into repeated bouts of circulatory collapse Fluid collected massively and rapidly in her peritoneal cavity. Her condition deteriorated rapidly, she passed into coma and died upon the eleventh postoperative day

Postmortem examination revealed advanced cirrhosis of the liver, extensive varices, and splenomegaly Sixteen thousand milliliters of fluid were present in her abdomen, and the lips of the shunt had sealed themselves together, completely occluding its stoma

Case #11 R S N.Y.H. #603,486 Male Aged 31 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Hematemesis

HISTORY R.S., a thirty-one year old marine who was wounded severely in the lower abdomen in 1944, was admitted to The New York Hospital in 1952 because of his second episode of hematemesis over a period of four months Otherwise, he was

but otherwise in apparent good health His liver was large and firm, and his spleen was readily palpable In the left lower abdomen was a well healed irregular celiotomy scar which had obviously healed by secondary intention Roentgenograms of his esophagus demonstrated extensive varices

OPERATION Four days after admission R S was operated upon and his portal bed decompressed by means of an end-to side portacaval shunt This reduced the portal pressure from 43 to 24 cm of saline

POSTOPERATIVE COURSE This was uneventful, and R S was discharged twelve days after operation He has not bled in the year and one-half since discharge, and varices cannot be detected in his esophagograms

Case #12 R M N Y H #609 430 Male Aged 48 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Hematemesis

HISTORY R M was admitted because of his first episode of hematemesis and tarry stools He claimed to have been well until one month before admission at which time he suddenly vomited a pint or so of bright red blood His liver was enlarged, and varices were demonstrated on roentgenograms of his esophagus

Case #9 M.S. N.Y.H. #545,952 Female Aged 16 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Hematemesis

HISTORY Seven years prior to admission, M.S. began having frequent bouts of epistaxis, and a year later hepatosplenomegaly was discovered Two years prior to admission she was jaundiced for several months, and a diagnosis of chronic hepatitis of unknown etiology was made About a month before admission, she experienced her first hematemesis Varices were demonstrated upon roentgen examination of the esophagus.

OPERATION. Six weeks after her hemorrhage, an end to-side portacaval shunt reduced her portal pressure from 34 to 16 cm. of saline.

POSTOPERATIVE COURSE. For several weeks after her operation she was again jaundiced, but left the hospital well fifteen days after operation

FOLLOW UP Although this young woman has not bled again in over two years, she has had two readmissions to another hospital in hepatic coma In one of these her serum bilirubin was 26 mg per 100 ml These bouts have subsided spontaneously, and the patient is now working

Case #10 M.A. N.Y.H. #601,270 Female Aged 43 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Persistent Gastrointestinal Bleeding

M.A., who had consumed generous amounts of whiskey daily for a number of years, was well until about five years prior to

appearance, and she obviously became frail and more chronically ill On admission to another hospital a diagnosis of cirrhosis was made, and she was found to be severely anemic. For a period of one week she was semi-comatose Upon regaining consciousness spontaneously, she was admitted to this hospital for further treatment

On admission M.A. was an ill woman, she was jaundiced, her liver was enlarged, and her spleen could be felt Extensive varices were demonstrated on x-ray examination and though she never bled massively, her stools were consistently positive for blood, and in spite of repeated transfusions her anemia persisted. It then became apparent to the patient, her husband, and her physicians that non-surgical therapy was of no avail, and she was

spleen were greatly enlarged Esophageal varices were demonstrated on an esophagogram

OPERATION On October 19, 1951, eighteen days after admission, an end to side portacaval shunt was performed which reduced the pressure in her portal venous system from 40 to 24 cm of saline.

POSTOPERATIVE COURSE This was uneventful and G.M was disch

lyte,

Case #15 P A N Y H. #120,190 Male Aged 58 years

Cirrhosis of the Liver (Laennec's), Portal Hypertension, Esophageal Varices, and Gastrointestinal Hemorrhage

P A was first suspected of having cirrhosis twelve years prior to his admission to the hospital because of repeated tarry stools For years he had used whiskey extensively Five years prior to

on several occasions his stools were persistently positive for blood, he became deeply jaundiced, and his abdomen had to be tapped on several occasions This long history culminated in a massive hematemesis and P A was admitted to the hospital

On admission P A was an acutely ill man His abdomen was distended and his skin icteric His blood pressure was 168/74 mm of mercury Esophageal varices were again demonstrated On multiple transfusions, high protein and low salt diet, P A improved and four weeks after admission he underwent an end-to-side portacaval shunt quite uneventfully This dropped his portal pressure from 48 to 34 cm of saline

P A s postoperative course was quite uneventful His jaundice

not be demonstrated, and he did not bleed At present, one year after operation, he is in reasonably good health.

Case #16 A K N Y H. #498,696 Female Aged 51 years

Cirrhosis of the Liver, Portal Hypertension, Esophagogastric Varices, Hematemesis, and Gastric Ulcer

Three months prior to admission H K, having been well all her life, had a massive hematemesis which subsided spontane-

OPERATION. An uneventfully performed portacaval shunt was fashioned in the end-to side position, reducing his portal pressure from 37 to 23 cm. of saline.

POSTOPERATIVE COURSE. Save for a transient period of atelectasis, R M 's course after operation was uneventful, and he was discharged three weeks later. He has been well during the fourteen months it has been possible to follow him after operation

Case #13 S M. N.Y H. #533,020 Female Aged 33 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Massive Hematemesis

HISTORY. For about three years prior to her admission because of a massive hematemesis, S.M had been followed in the Liver Clinic of The New York Hospital for cirrhosis. She had consumed large amounts of beer intermittently for about five years prior to admission About a year prior to her massive hematemesis, an esophagogram had been negative, but on repeating this study soon after her admission varices were demonstrated.

PHYSICAL EXAMINATION On admission S.M. was chronically but not acutely ill She had numerous spider angiomas, liver palms, and a large firm liver was palpated three fingerbreadths below the right costal margin. On supportive measures her general condition improved greatly over the course of the next twenty-eight days

OPERATION Twenty eight days after admission, an end-to side portacaval shunt was performed. This reduced her portal pressure from 39 to 20 cm of saline.

POSTOPERATIVE COURSE Except for a low-grade fever for the first ten postoperative days, her course was uneventful and she was discharged eighteen days after operation S M has been followed regularly for eighteen months after discharge. She has retained her weight and strength, has not bled again, and her esophagograms fail to reveal evidence of varices

Case #14 G M N Y H #484,088 Female Aged 51 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Massive Hematemesis

HISTORY G M was known to The New York Hospital to have had cirrhosis for at least four years prior to admission During this period, she had been continually under observation and

PHYSICAL EXAMINATION G M was a thin, poorly nourished white female with numerous spiders over her upper arms and chest. Her blood pressure was 130/75, and both her liver and

numerous large varices were demonstrated on an esophagogram Blood pressure was 125/85

PREOPERATIVE COURSE Certainly J McE was in liver failure

and his jaundice

considered to be in sufficiently good condition to withstand portal decompression

OPERATION. On March 18, 1952, eight weeks after admission, an end-to-side portacaval shunt was performed *uneventfully* The portal pressure was 50 cm of saline This fell to 20 cm of saline after the shunt was opened

POSTOPERATIVE COURSE. This was quite uneventful, and J McE

ascites was reappearing Readmission was refused, *and in her* next report his wife stated that her husband died three weeks after discharge from the hospital

COMMENT In retrospect, it is obvious that this man was helped but little by his operation If it had been possible to assess

in attempting to evaluate patients with advanced cirrhosis for portal decompression J McE's preoperative and postoperative water electrolyte, and protein chart is reproduced in Figure 108, page 313

Case #18 H G N Y H #628,256 Male Aged 55 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Hematemesis

For thirty four years H G had been a persistent alcoholic Two years prior to admission a diagnosis of cirrhosis was made upon a basis of weakness, fatigue, and a large liver The day before admission he vomited large amounts of blood and was admitted to this hospital in a precarious state He responded nicely to transfusion therapy, and three weeks *after admission a*

came comatose From this point on, he failed daily and died two weeks later A postmortem examination revealed an advanced

ously. A gastrointestinal series was said to have demonstrated a gastric ulcer and operation was advised. A.K. refused this and came to The New York Hospital for advice. A diagnosis of cirrhosis of the liver and portal hypertension was made. Esophageal varices were demonstrated, and she was admitted for operation. At an exploratory celiotomy her portal pressure was 32 cm. of saline. In addition an adenomatoid mass (later proved to be a healed gastric
lesion proved
shunt was fash
of saline

A.K.'s postoperative course was uneventful, and she was discharged nineteen days after operation. Four months later she was readmitted and a subtotal gastrectomy for a gastric ulcer was performed. At this time her portal pressure was 11 cm. of saline, and a widely patent shunt was demonstrated by the injection of 70 per cent Diodrast into the superior mesenteric vein. (Portal venogram in Fig. 92, p. 278.) Her postoperative course was complicated by anemia, a leukomoid reaction, and a transient bout of jaundice. From these she recovered slowly and was discharged well six weeks after admission. She has had one episode of hepatic coma precipitated by overwork and failure to eat regularly. She recovered promptly on hospitalization. One year following operation she is reasonably well and working regularly.

Case #17 J.McE. N.Y.H. #620,310 Male Aged 50 years

Cirrhosis of the Liver, Portal Hypertension, and Esophageal Varices with Massive Hemorrhage. Jaundice. Abdominal Ascites

HISTORY. J.McE. was admitted to The New York Hospital in January of 1952 because of jaundice, abdominal swelling, hematemesis, and tarry stools. He dated the onset of his illness to six months prior to admission at which time his appetite became poor and he began having mild nasal hemorrhages several times a week. Two months prior to admission he became jaundiced and a month later experienced his first massive hematemesis. This ceased spontaneously and though the patient improved somewhat after multiple transfusions, he shortly developed massive abdominal ascites and his jaundice deepened. Only temporary relief was obtained from repeated paracenteses. J.McE. habitually drank four to five highballs daily.

PHYSICAL EXAMINATION. On admission the patient appeared acutely and chronically ill. There was obvious muscle wasting, he was jaundiced, and there were numerous spider hemangiomas over his face, chest, and upper arms. His abdomen was distended with fluid. His liver and spleen were palpably enlarged, and

cirrhosis of the liver. From time to time he was jaundiced and had varying degrees of ascites On three occasions he had violent hematemesis which ceased upon tamponade After each of the first two episodes, portal decompression was refused, this was accepted after a third exsanguinating hematemesis and was successful in lowering his portal pressure from 34 to 19 cm of saline

Seventeen days after operation F G was discharged well and has remained so for the ensuing six months.

Case #21 W.K N Y H #481,204 Male Aged 57 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Hematemesis

For many years W K had eaten poorly and reportedly drank

and pass blood stools On admission W K was pale and lethargic *His liver extended well below his right costal margin*, and many large varices were demonstrated on esophagography After proper blood replacement, a portacaval anastomosis was performed in the end-to side position, reducing his portal pressure from 35 to 20 cm of saline (Portal venogram in Fig 88, p 275) His postoperative course was quite uneventful After

ing the four month follow up period (See note, p 379)

Case #22 O A Knickerbocker Hospital #44,899* Male Aged 24 years

Cirrhosis of Liver (Schistosomal), Portal Hypertension, Esophageal Varices, and Hematemesis

O A, a twenty four year-old Puerto Rican, had experienced repeated bouts of hematemesis, tarry stools, and weakness over a period of six years prior to admission Otherwise his history was negative

On admission O A was pale and chronically ill Both his liver and spleen were palpable A stool specimen was positive for ova of Schistosoma mansoni, and esophageal varices were identified on esophagoscopy and esophagograms

On the evening of admission O A vomited approximately 2 liters of blood Further hemorrhage was controlled by tamponade, and the bleeding ceased after three days

One month after admission an end to side portacaval shunt reduced his portal pressure from 30 to 24 cm of saline His

* Included in this series through the courtesy of Dr Russel H Patterson

degree of cirrhosis, a patent shunt, bronchopneumonia, and pyemia.

Case #19 H.M. N.Y.H. #403,157 Male Aged 49 years
Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Hematemesis

For about thirty years, H.M. had consumed about a quart of wine a day. This was without known ill effect until about eight years prior to admission when he began to vomit daily before breakfast. This lasted several months, and H.M. was quite well until a year prior to admission when he began to lose his appetite and weight, developed a chronic cough, and a mild erythem-

vomited a copious amount of dark blood and passed a large tarry stool. Several more hemorrhages occurred before he was sent to the hospital by his local physician.

On admission H.M. was a well developed, obese, white male

ing subsided spontaneously, and his general appearance improved after several transfusions. Esophageal varices were demonstrated roentgenographically.

A month after admission the patient was taken to the operating room for a portal decompression. Throughout the procedure bleeding from the wound edges was copious. In fact, this was so profuse that at one point the advisability of proceeding was challenged. Under great handicaps, however, and supported by 4000 ml. of citrated blood, an end to side portacaval shunt was fashioned which lowered the portal pressure from 40 to 20 cm of saline. Upon transferring H.M. to the recovery room, his arterial blood pressure fell to 80/50, and in spite of vigorous therapy, including additional transfusions, he failed to recover consciousness and died four hours after operation. Just before death, his abdomen was reopened and a huge amount of blood found free in the peritoneal cavity. Part of this at least appeared to be coming from edges of the anastomosis between the portal vein and the vena cava.

Case #20 F.G. N.Y.H. #600,949 Male Aged 48 years
Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Hematemesis

F.G., an accomplished actor and an alcoholic, was known for one year to The New York Hospital as a patient with advanced

the fact that the portal pressure fell only from 42 to 41 cm of saline. It was the operator's opinion that failure to secure a more impressive fall was due to imperfect manometry rather than to

gram was suspicious but not diagnostic of varices

Case #25 F M N Y H #643,089 Male Aged 53 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Massive Hematemesis

HISTORY. F M. had progressive swelling of his abdomen requiring paracenteses for two years prior to his admission to The New York Hospital An exploratory celiotomy revealed cirrhosis of the liver with a granulomatous lesion thought to have been tuberculosis Treatment with streptomycin and PAS was administered He denied an excessive alcoholic intake but was known to have worked with chloroform daily for five years He had one major hematemesis four months prior to hospitalization and another on the day of admission

PHYSICAL EXAMINATION F M was an emaciated male acutely

Each time this was deflated he bled again and lapsed into coma On the thirteenth day after admission he was taken to the operating room with the balloon inflated in the esophagus

OPERATION On December 16, 1952 a portacaval shunt was performed which reduced the portal pressure in his portal venous system from 28 to 22 cm of saline

POSTOPERATIVE COURSE The postoperative course was marked by fever and jaundice The patient bled from his lower bowel, but no blood was recovered from the stomach or upper bowel He was sustained with transfusions and gradually recovered sufficiently to leave the hospital

FOLLOW UP It was necessary to reexplore this patient two months later because of an abdominal mass and continued fever A loculated infected collection of ascitic fluid was drained His course is further complicated at present by the development of homologous serum jaundice four months after operation (See note, p 379)

Case #26 R S N Y H. #465,832 Female Aged 56 years

Cirrhosis of the Liver, Portal Hypertension, and Massive Hematemesis

HISTORY R S had been passing tarry stools and vomiting bright red blood daily for the two weeks preceding her hospital

postoperative course was uneventful, and O.A. was discharged on his twelfth postoperative day. He has remained well during the twelve months it has been possible to follow him.

Case #23 F.S. N.Y.H. #639,657 Male Aged 51 years

Cirrhosis of the Liver, Esophageal Varices, Portal Hypertension, and Hematemesis

HISTORY F.S., a fifty-one-year-old white male, was admitted to the hospital a month or so after his third episode of hematemesis. Although he had been admitted to a hospital during each of these episodes and studied extensively, a cause for his bleeding was not demonstrated until shortly before this admission when esophageal varices were demonstrated. For many years he had used alcohol extensively.

PHYSICAL EXAMINATION F.S. was an obese, hale and hearty

caval shunt was fashioned. This dropped his portal pressure from 46 to 26 cm. of saline.

POSTOPERATIVE COURSE This was uncomplicated, and the patient was discharged twenty-five days after operation. He has been followed five months and has been well; hematemesis has not recurred.

Case #24 G.B. N.Y.H. #642,457 Male Aged 42 years

Cirrhosis of the Liver, Esophageal Varices, Portal Hypertension, and Massive Hematemesis

G.B. had consistently consumed alcohol for many years. For

red blood and was brought to the emergency service.

During the first twelve hours after admission G.B. vomited about 3 liters of blood, and he was kept out of shock only by the generous exhibition of citrated blood. Two days after admission a subtotal gastrectomy was performed. This was unfor-

vanced cirrhosis.

On the thirteenth, fourteenth, and fifteenth postoperative days G.B. vomited small amounts of blood. One month after his subtotal gastrectomy, an end-to-side portacaval shunt was fashioned. This appeared to be functioning satisfactorily in spite of

Case #28 B.W. N Y H #649,064 Female Aged 55 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Hematemesis

HISTORY B W has had a poor diet and a high daily alcoholic intake for many years Except for ankle edema, she was well until her first hematemesis five weeks prior to admission She came to The New York Hospital when this bleeding recurred

PHYSICAL EXAMINATION B W was a pale, obese woman chronically ill Both the liver and the spleen were enlarged A moderate amount of ascites was present Esophageal varices were demonstrated on x ray

OPERATION On March 16, 1953, thirty four days after admission, an end to-side portacaval shunt was performed which reduced her portal pressure from 51 to 27 cm of saline

POSTOPERATIVE COURSE This was complicated by the development of a low salt syndrome when ascitic fluid was removed and by the presence of osteomyelitis of the finger At present she is improving slowly at home and visits the clinic regularly for control of the ascitic fluid and the edema

Case #29 M P N E C H #67-488 Male Aged 57 years

Portal Hypertension due to Cirrhosis Portacaval Shunt

This fifty-seven-year old Italian was known to have had cirrhosis of the liver for many years During the six months prior to admission, he suffered two massive hematemeses requiring hospitalization and multiple transfusions Although he had used alcohol steadily over many years, he had never been jaundiced nor had he had ascites On admission physical examination disclosed a well developed and well nourished man in apparent fair health There was minimal muscle wasting, erythema of the palms, and hypertrophic ostearthropathy of the distal phalanges of all fingers The liver and spleen were both palpably enlarged, and over the anterior abdominal wall there were many collateral veins Laboratory examination disclosed a hemoglobin of 12 9 grams, Bromsulphalein retention of 13 per cent and a serum bilirubin of 0 8 mg per 100 ml His total protein was 6 6 grams per 100 ml with a serum albumin of 3 8 and serum globulin of

f the lower

an explora

tory celiotomy A portal venogram demonstrated a normal portal vein Two small areas of radiolucency suggested small thrombi on the wall of the portal vein (Portal venogram in Fig. 90, p 276) The portal pressure was 49 cm of saline After the portal vein was freed from the other structures in the hepatoduodenal

admission Prior to this, over a five-year period, she had expe

for many years

PHYSICAL EXAMINATION On admission R.S was a moderately obese white female, both acutely and chronically ill. There were several spider angiomas on the chest, the scleras were icteric, the liver and spleen were greatly enlarged, and there was a 1 plus edema of the ankles

COURSE R S continued to bleed while in the hospital, developed marked ascites, and went into coma. Her bleeding was only partially controlled by the esophageal balloon. On the twentieth hospital day she was taken to the operating room for portal decompression with the balloon inflated in the esophagus.

OPERATION On January 5, 1953, an end to-side portacaval shunt was performed which reduced the pressure from 32 to 21 cm of saline

POSTOPERATIVE COURSE On the second postoperative day the balloon was removed. There was no more bleeding throughout her course. However, her urinary output remained below 200 cc. per day. She lapsed into coma and died on the fifth postoperative day

Case #27 C S N Y H. #647,350 Male Aged 29 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, and Massive Hematemesis

HISTORY C S came to The New York Hospital because of repeated massive hematemeses over a five-year period A diagnosis of cirrhosis of the liver and portal hypertension had been established five years previously at an exploratory celiotomy. A splenectomy had been done at that time, but bleeding continued

PHYSICAL EXAMINATION C S was a thin male not appearing ill. His liver extended one fingerbreadth below the costal margin. Esophageal varices were demonstrated on an esophagogram.

OPERATION On January 28, 1953, an end to-side portacaval shunt was performed which lowered the pressure in the portal bed from 24 to 12 cm of saline.

POSTOPERATIVE COURSE This was uneventful, and he was discharged on the thirteenth postoperative day

FOLLOW UP No further bleeding has occurred The patient feels well and has been back at work for the past four months.

FOLLOW-UP. No further bleeding has occurred The patient feels well and has been back at work for the past four months

SPLENORENAL SHUNTS

Case #1 D R N Y H. #576,553 Female Aged 15 years

Extrahepatic Block, with Portal Hypertension, Splenomegaly, Esophageal Varices, and Repeated Hematemeses

HISTORY D R, a fifteen-year-old school girl, was admitted to the hospital in July of 1950 because of severe hematemesis and tarry stools For several years prior to admission this youngster

became associated with weakness, headaches, and dizziness Three weeks prior to admission she began to pass tarry stools

though

below

an emergency tracheostomy had to be performed After a stormy course of a week or so, the balloon was removed and she recovered nicely

FIRST OPERATION Three weeks after admission an inflammatory extrahepatic portal block was demonstrated at the foramen of Winslow Splenectomy was performed and a splenorenal shunt fashioned in the end-to-side position This did not effectively lower the portal pressure which was 40 cm of saline Microscopic examination of the inflammatory mass and the spleen suggested a diagnosis of tuberculosis

POSTOPERATIVE COURSE This was uneventful, and D R was discharged four weeks after operation

FOLLOW UP *D R returned to the hospital within six months*

ligament, it was divided close to the base of the liver. The previously suspected thrombi were identified and simply peeled off the endothelial surface. A satisfactory portacaval shunt was obtained in the end-to-side position The portal pressure dropped to 30 cm. of saline.

BIOPSY OF THE LIVER The specimen was reviewed by Dr. MacMahon who felt that the pathological changes in this man's liver could best be interpreted as healed hepatitis.

POSTOPERATIVE COURSE. The postoperative course was uneventful, and the patient was discharged upon his thirteenth postoperative day He has been entirely well for five months.

Case #30 J.E. N.E.C.H. #75-446

Alcoholic Cirrhosis, Portal Hypertension, Esophageal Varices, and Hematemesis

J.E., a sixty-three-year-old married man who had consumed large amounts of alcohol over many years, was admitted because of four massive hematemeses during the year prior to admission. Associated with this primary complaint, J.E. noticed that he fatigued easily and that he was losing weight.

Physical examination revealed a chronically ill, flabby white male. There was one large spider over his left shoulder, muscle wasting was obvious, his liver and spleen were both palpably enlarged, and the veins over his anterior abdominal wall were enlarged Ascites could not be detected, but there was edema of both ankles

LABORATORY Hemoglobin was 10.8 grams, red blood cells 3.72, white blood cells 6400, urinalysis negative. Serum bilirubin was 1.6 mg per 100 ml., total protein 6.7 grams per 100 ml, albumin 3.7 and globulin 3.0.

ROENTGEN EXAMINATION Esophagogram revealed esophageal varices, and calculus disease of the biliary tract was demonstrated on cholecystography

OPERATION. Portacaval shunt, end-to-side, portal venography, and biopsy of the liver were performed. The portal pressure was 35 cm. of saline. A post-shunt pressure of 45 cm of saline was obtained, but it was hoped that this was a technical error.

PATHOLOGICAL DIAGNOSIS (Dr H. E. MacMahon). Alcoholic cirrhosis, chronic and active This was far advanced and associated with an almost complete disappearance of the portal system of veins

POSTOPERATIVE COURSE His postoperative course was uneventful, and he was discharged upon his seventeenth day after operation A postoperative esophagogram failed to demonstrate varices and the patient has been well for four months.

gency celiotomy at which time her portal pressure was measured at 48 cm of saline. This information together with the repeated demonstration of large esophageal varices led to the conclusion that the splenorenal shunt had closed A second attempt at portal decompression was considered essential

SECOND OPERATION At this time a portal venogram (Fig 84, p 272) demonstrated a large and patent superior mesenteric vein An autogenous venous graft was successfully inserted between this and the superior vena cava Although this was patent at its completion, the portal pressure changed only slightly, rising from 34 to 42 cm of saline

POSTOPERATIVE COURSE This was uneventful and P R was discharged sixteen days after insertion of the venous graft

FOLLOW-UP In the year since operation, this patient has not done well Her varices are still present, she has had one minor episode of bleeding, and a severe behavior problem has contributed to her other difficulties

Case #4 H K N Y H #603,401 Male Aged 56 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, Splenomegaly, and Hematemesis

H K, a white male of Turkish extraction, had never used alcohol and had considered himself in excellent health until five months prior to admission when he suddenly vomited copious amounts of blood and was admitted to another hospital The bleeding ceased and an exploratory celiotomy established a diagnosis of portal hypertension Following operation, H K developed ascites and ankle edema One month later he bled again, and his ascites increased For several months he was treated in the Liver Clinic of The New York Hospital, and his ascites subsided Extensive varices were demonstrated in his esophagogram (see Fig 73 A, p 227)

Six months after his first hemorrhage, he was admitted for an elective portal decompression Because of a hugely enlarged spleen and a splenic vein of generous size, an end to-side splenorenal shunt was performed This reduced his splenic venous pressure from 30 to 18 cm of saline His postoperative course was uneventful, and H K has been well during the year and one half he has been followed since operation An esophagogram performed three months after operation failed to reveal evidence of varices (see Fig 73 B)

SUPERIOR MESENTERIC-VENA CAVAL SHUNT

Case #1 E T N Y H #147 136 Male Aged 35 years

Cirrhosis of the Liver, Esophageal Varices and Hematemesis

HISTORY E T was first seen at The New York Hospital when he was twenty one years of age His reason for seeking medical

bilateral vagotomy accompanied this operation, a Finney type pyloroplasty was added to the operative procedure (Fig 78, p. 259).

POSTOPERATIVE COURSE This was complicated by fever of undetermined origin which slowly subsided, and she was discharged on the thirty-fifth day after operation

FOLLOW UP. From time to time D.R. returned to the clinic reporting that she was slowly improving. She has not bled in the year and one-half since her second operation Interestingly enough, a late postoperative esophagogram fails to reveal varices (Fig 79 A and B, p. 260).

Case #2 W D. N Y H #594,319 Male Aged 5½ years

Extrahepatic Portal Block, Splenomegaly, Portal Hypertension, Varices, and Hematemesis

At six weeks of age, W.D. was ill with a high fever and an infected umbilicus This subsided spontaneously, and he was well until a year before admission when he had a severe hematemesis This was repeated a day or so later and became associated with a fever of 104° F A diagnosis of bronchopneumonia was made. Another hematemesis occurred several weeks prior to admission, and films of his esophagus disclosed large varices.

Seventeen days after admission, an enlarged spleen was removed and his portal bed decompressed by means of an end-to-end splenorenal shunt. This reduced his portal pressure from 47 to 34 cm of saline W D's postoperative course was uneventful, and he was discharged six weeks after operation

He has been followed for two years and has been well and active.

Case #3 Superior mesenteric-vena caval (graft) #2 P.R. N.Y H #598,106 Female Aged 14 years

Extrahepatic Portal Block, Splenomegaly, and Esophageal Varices

HISTORY. This fourteen-year-old schoolgirl was admitted to this hospital because of splenomegaly and anemia. On esophagography the roentgenologists demonstrated extensive varices. She had not bled from her varices.

FIRST OPERATION. At operation an extensive extrahepatic portal obstruction was demonstrated and splenectomy was performed. This was followed by an end-to side splenorenal shunt which reduced her portal pressure from 42 to 23 cm. of saline

POSTOPERATIVE COURSE This was uneventful and P R was discharged to the clinic eighteen days after operation.

FOLLOW-UP. Six months after operation, she returned to the hospital because of an acute intestinal obstruction due to postoperative adhesions. These were successfully divided at an emer-

gency celiotomy at which time her portal pressure was measured at 48 cm of saline This information together with the repeated demonstration of large esophageal varices led to the conclusion that the splenorenal shunt had closed A second attempt at portal decompression was considered essential

SECOND OPERATION At this time a portal venogram (Fig 84,

ing from 34 to 42 cm of saline

POSTOPERATIVE COURSE This was uneventful and P R was discharged sixteen days after insertion of the venous graft

FOLLOW-UP In the year since operation, this patient has not done well Her varices are still present, she has had one minor episode of bleeding, and a severe behavior problem has contributed to her other difficulties

Case #4 H K N Y H #603,401 Male Aged 56 years

Cirrhosis of the Liver, Portal Hypertension, Esophageal Varices, Splenomegaly, and Hematemesis

H K, a white male of Turkish extraction, had never used alcohol and had considered himself in excellent health until five months prior to admission when he suddenly vomited copious amounts of blood and was admitted to another hospital The bleeding ceased and an exploratory celiotomy established a diagnosis of portal hypertension Following operation, H K developed ascites and ankle edema One month later he bled again, and his ascites increased For several months he was treated in the Liver Clinic of The New York Hospital, and his ascites subsided Extensive varices were demonstrated in his esophagogram (see Fig 73 A, p 227)

Six months after his first hemorrhage, he was admitted for an elective portal decompression Because of a hugely enlarged spleen and a splenic vein of generous size, an end to side splenorenal shunt was performed This reduced his splenic venous pressure from 30 to 18 cm of saline His postoperative course was uneventful, and H K has been well during the year and one half he has been followed since operation An esophagogram performed three months after operation failed to reveal evidence of varices (see Fig 73 B)

SUPERIOR MESENTERIC-VENA CAVAL SHUNT

Case #1 E T N Y H #147,136 Male Aged 35 years

Cirrhosis of the Liver, Esophageal Varices, and Hematemesis

HISTORY E T, was first seen at The New York Hospital when he was twenty one years of age His reason for seeking medical

attention at that time was repeated bouts of hematemesis and tarry stools. A diagnosis of Banti's disease was made, and an enlarged spleen removed. Over the course of the next fourteen years he bled severely every two to three years. These episodes were never catastrophic, and after a transfusion or two he returned each time to work. In 1950, however, a severe episode of hemorrhage precipitated his admission to the hospital for another try at portal decompression. X-rays of his esophagus at this time revealed extensive varices.

OPERATION. Because this man's portal vein was short and sclerotic and because of a large caudate lobe obstructing the site at which a portacaval shunt would have had to be performed, an end to side shunt was fashioned between the superior mesenteric vein and the vena cava. This elevated his portal pressure from 36 to 38 cm. of saline.

POSTOPERATIVE COURSE. This man bled several times during the immediate postoperative period but was finally discharged well three months after operation.

FOLLOW-UP. E.T. has been followed over a period of three years since his shunt and has bled intermittently. These episodes have not been severe, the patient has continued to work, and he has preferred not to have further efforts made to control his bleeding. Repeated films of his esophagus have demonstrated varices.

SHUNT IMPOSSIBLE

Case #1 A.B. N.Y.H. #353,465 Male Aged 55 years

Cirrhosis of the Liver, Hemochromatosis, Portal Hypertension, Esophageal Varices, and Hematemesis

A.B. had been followed in this hospital for six years prior to his terminal illness. His first admission, for epigastric pain of five years' duration, culminated in a diagnosis of hepatomegaly,

[illegible]

diagnosis included hemochromatosis of skin, liver, and pancreas,
xeroderma pig[illegible]
cholecystitis [illegible]
bled again. His [illegible]
hospital and after a few weeks he was admitted to The New York Hospital primarily for weakness, excessive fatigue, and persistent *hepatic pain*

On admission A.B. was deeply bronzed. His blood pressure was 140/86. His liver and spleen were enormously enlarged. Because of the persistent pain, a diagnosis of cancer of the liver was entertained, and A.B. was transferred for exploratory celiotomy.

At operation an enormous hydrops of the gallbladder precluded portal decompression. A cholecystectomy was performed. His portal pressure was 48 cm. of saline, but in view of his precarious condition a shunt was *not* attempted. Save for hemochromatosis and cirrhosis, his liver was negative.

Postoperatively, A.B. did poorly, bled massively on several occasions, and died on the third day after operation.

Case #2. E.C. N.Y.H. #509,430. Female. Aged 55 years.

Cirrhosis of the Liver, Chronic Cholecystitis, Choledocholithiasis, Portal Hypertension, Thrombosis of the Portal Vein, and Hematemesis

Ten years before admission E.C. experienced an attack of

passed numerous tarry stools. Six months later hematemesis again occurred, and two years later the third and admitting episode of esophageal hemorrhage occurred.

On admission E.C. was desperately ill, jaundiced, and obviously in precarious health. She continued to bleed and because hemorrhage could only be controlled by tamponade, she was subjected to an exploratory celiotomy in the hope that portal decompression could be effected. At operation the liver was found to be the site of advanced cirrhosis, and many stones were present in the common duct. This structure was enlarged and adherent to the portal vein. In attempting to mobilize this vessel, it was found to be completely thrombosed and obviously useless for purposes of portal decompression. The stones were removed from the common duct, and a T tube was left in place.

Postoperatively E.C. did well save for a transient period of disorientation suspected of being liver coma, and was discharged three and a half weeks after operation. Five months later, she was admitted because of further esophageal hemorrhage. This could not be controlled by tamponade, and E.C. died. A postmortem examination confirmed the presence of cirrhosis and many large esophageal varices, one of which was ulcerated.

attention at that time was repeated bouts of hematemesis and tarry stools A diagnosis of Banti's disease was made, and an enlarged spleen removed. Over the course of the next fourteen years he bled severely every two to three years. These episodes were never catastrophic, and after a transfusion or two he re-

time revealed extensive varices.

OPERATION. Because this man's portal vein was short and sclerotic and because of a large caudate lobe obstructing the site at which a portacaval shunt would have had to be performed, an end to-side shunt was fashioned between the superior mesenteric vein and the vena cava This elevated his portal pressure from 36 to 38 cm. of saline.

POSTOPERATIVE COURSE. This man bled several times during the immediate postoperative period but was finally discharged well three months after operation.

FOLLOW-UP. E T has been followed over a period of three years since his shunt and has bled intermittently. These episodes have not been severe, the patient has continued to work, and he has preferred not to have further efforts made to control his bleeding Repeated films of his esophagus have demonstrated varices.

SHUNT IMPOSSIBLE

Case #1 A B N Y.H. #353,465 Male Aged 55 years

Cirrhosis of the Liver, Hemochromatosis, Portal Hypertension, Esophageal Varices, and Hematemesis

A B had been followed in this hospital for six years prior to his terminal illness His first admission, for epigastric pain of five years' duration, culminated in a diagnosis of hepatomegaly, splenomegaly, and hemochromatosis. A year or so later he was found to have a non functioning gallbladder and mild diabetes Three years prior to admission he had his first of several bouts of hematemesis and esophageal varices were demonstrated. A

xeroderma pigmentosum, acute fibrinous pleurisy, and chronic cholecystitis. After a few months of reasonable good health, he bled again. His shock, due to blood loss, was treated in another hospital and after a few weeks he was admitted to The New York Hospital primarily for weakness, excessive fatigue, and persistent hepatic pain

to bleed in spite of presumably adequate balloon tamponage and massive transfusions. She died in shock twenty-four hours postoperatively

LIVER BIOPSY Essentially normal

AUTOPSY. The important features were a huge number of varices extending the entire length of the esophagus These were punctured in at least a dozen places by small ulcerations, from at least three of which the patient had obviously bled The portal and splenic veins were thrombosed and only minimally visual-

cessful

NOTE Recently (November 1, 1953) additional information has been obtained upon the following patients in this series

Case #2 D M N Y H #466,182 This man died exactly three years after operation of a primary carcinoma of the liver He did not bleed during this period and at postmortem examination the shunt was patent

Case #3 J R N Y H #582,110 This man died in coma two and one-half years after operation He did not bleed during this period

Case #4 D K N Y H #582,973 This woman died of a carcinoma of the lung *with extensive hepatic metastases two years* and eight months after operation Her shunt was patent and though a few varices were present, she did not bleed postoperatively

Case #21 W K *N Y H #484,204* This man died in coma nine months after operation No recurrent hemorrhage

Case #25 F M N Y H #643,089 This man never recovered from his homologous serum jaundice and died six and one half months after operation

Case #3 E.L. N.E.C.H. #75-431

Extrahepatic Block due to Thrombosis of Portal, Superior Mesenteric, and Splenic Veins (? Postcholecystectomy)

Mrs E.L., aged sixty-seven, was admitted because of persistent massive hematemesis of approximately three weeks' duration She stated that five years prior to admission she underwent an uneventful cholecystectomy. Eight months later she experienced her first episode of massive hematemesis. This repeated itself annually, and though she was studied extensively on each of these occasions, a satisfactory explanation for the hemorrhages was never reached During her present episode, she bled so consistently that thirty pints of blood were required for control.

On admission Mrs. E.L. was pale and apprehensive but not in shock Her pulse was 80, respirations 20, and blood pressure 140/70. General physical examination was negative except for a *well healed right upper rectus incision Neither the liver nor the* spleen was palpable Ascites could not be detected or was there

[illegible]

lin 2 6, serum bilirubin 2 0 The stools were consistently positive for blood. Bromsulphalein was 33 per cent retention and cephalin flocculation 1 plus

ROENTGEN EXAMINATION. An emergency esophagogram (Fig. 71, p 213) revealed huge varices extending from the pharynx down to the gastric cardia.

COURSE The day after admission, this patient had another massive hematemesis which was controlled by a Blakemore-Sengstaken balloon. Because of the great extent of esophagus involved in varix formation, any idea of transesophageal ligation was abandoned

OPERATION With the balloon in place, the patient was taken to the operating room, hoping that portal decompression might be accomplished On opening the abdomen, the liver was grossly normal and the spleen enlarged about two times There were huge anastomoses between the spleen and the lateral abdominal wall. The portal pressure was 43 cm of saline A portal venogram revealed a complete extrahepatic block, and the splenic vein could not be visualized (Fig. 85, p. 273). It was concluded, therefore, that neither the portal nor splenic vein was available for shunting purposes Since this patient's condition was precarious, any thought of decompression by means of an autogenous graft was likewise abandoned. Because of the enormous perisplenic collateral circulation, splenectomy was considered unwise. The abdomen was closed in defeat

POSTOPERATIVE COURSE. *This patient did poorly. She continued*

BIBLIOGRAPHY

——— Longman, Hurst
d by O D Cooke,
1825

Abdou, I A, Reinhardt, W O, and Tarver, H Plasma Protein III The Equilibrium between Blood and Lymph Protein J Biol Chem, 194 15–23, 1952

Adams, H D Treatment of Portal Hypertension and Associated Acute Hemorrhage S Clin North America, 28 803–813, 1951

Adams, L A, and Levy, S Comparative Anatomy New York, John Wiley & Sons, 1949

Adlersberg, D, and Fox, C L Changes of the Water Tolerance Test in Hepatic Disease Ann Int Med, 19 642–650, 1943

Ahrens, E H, Jr Payne, M A, Kunkle, H G, Eisenmenger, W J, and Blondheim S H Primary Biliary Cirrhosis Medicine 29 299–361, 1950

Akrawi, velopment and
-luded Arteries

Allison
Altmeie
Amatu, Blood Pyruvic
cose or Insulin
in the Normal and in Patients with Liver Disease and with Diabetes Mellitus J Clin Investigation, 31 751–754, 1952

——— Stutzman, F L, Shrifter, N, and Nesbit, S A Study of Serum Electrolytes (Na, K Ca, P) in Patients with Severely Decompensated Portal Cirrhosis of the Liver J Lab & Clin Med, 39 26–28, 1952

Anderson, A H and Povlsen, O Occlusion of Afferent Vessels of the Liver Nord med 44 1091–1094, 1950.

Andrews W H H, and Maegraith, B G. The Pathogenesis of the Liver Lesion due to the Administration of Carbon Tetrachloride Ann Trop. Med, 42 95–100, 1948

Andrus W deW Personal Communication

——— and Holman, C W · Splenectomy in Various Blood Disorders Ann Surg 109 64–80, 1939

Arey L B On the Presence of the So-Called Portal Lobules in the Seal's Liver, Anat Rec, 51 315–322, 1932

——— Throttling Veins in the Livers of Certain Mammals Anat Rec, 81· Supp pp 21–30, 1941

Bartlett, F K, Corper, H J, and Long, E R The Independence of the Lobes of the Liver Am J Physiol, 35 36–50, 1914
Bateman, J C., Shorr, H M, and Elgvin, T Hypervolemic Anemia in Cirrhosis J Clin Investigation, 28 539–546, 1949
Baudouin, M The Ligature of the Hepatic Artery Ann internat de chir gastro intest, 3 39–42, 1909
Bauer, A In the Intrahepatic Venous Circulation Arch de med expér et d'anat path, 22 1–16, 1910
Bauer, W, Dale, H H, Poulsson, L T, and Richards, D. W The Control of Circulation through the Liver J Physiol, 74 343–375, 1932.
Baxter, J H, and Ashworth, C T Renal Lesions in Portal Cirrhosis Arch Path, 41 476–488, 1946
Bayliss, W M, and Starling E H Observations on Venous Pressures and Their Relationship to Capillary Pressures J Physiol, 16 159–202, 1894
Beale, L S The Liver London, J and A Churchill, 1889
——— On Some Points in the Anatomy of the Liver of Man and Vertebrate Animals London, J Churchill, 1856
——— On the Lymphatics of the Liver Arch Med, I 113–115, 1858
Bean, W B, Franklin M, Embick, J F and Daum, K Absorption Studies Using Portal Anastomotic Veins J Clin Investigation, 30 263–273 1951
Bearn, A G, Billing, B, and Sherlock S The Effect of Adrenaline and Noradrenaline on Hepatic Blood Flow and Splanchnic Carbohydrate Metabolism in Man J Physiol, 115 430–440, 1951
Beattie, A S, and Hildebrand, E Thrombosis of the Hepatic Veins Arch Path 50 247–254 1950
Beck, J S P, and Berg, B N The Circulatory Pattern in the Islands of Langerhans Am J Path 7 31–35, 1931
Beer, E Ligation of the Portal Vein in Suppurative Portal Phlebitis Am J M Sc, 150 548–555, 1915
Belt, A E, Smith, H P, and Whipple G H III Factors Concerned in the Perfusion of Living Organs and Tissues Artificial Solutions Substituted for Blood Serum and the Resulting Injury to Parenchymal Cells Am J Physiol, 52 101–119, 1920
Benz, E J, Baggenstoss, A H, and Wollaeger, E E Atrophy of the Left Lobe of the Liver Arch Path 53 315–330 1952
Berg B N A Study of the Islands of Langerhans in Vivo with Observations on the Circulation Am J Physiol, 95 186–189 1930
Berger, E Y and Steele, J M Suppression of Sodium Excretion by the Colon in Congestive Heart Failure and Cirrhosis of the Liver Demonstrated by the Use of Cation Exchange and Resins J Clin Investiga

The Adrenal and Early
8–264, 1947
, 1951

——— Personal Communication
——— and Hull, J E Hepatic, Splenic and Left Gastric Arterial Ligations in Advanced Portal Cirrhosis Arch Surg 65 37–64, 1952
Bernard, C Experimental Evaluation of the Glycogenic Function of the Liver Compt rend Acad de sc, 84 1201–1207, 1877
——— Veins Establishing a Direct Communication between the Portal Vein and the Inferior Vena Cava Compt rend Soc de biol, 1 87, 1849

Arey, L. B., and Simonds, J. P. The Relation of the Smooth Muscle in the Hepatic Veins to Shock Phenomena. Anat. Rec., 18:219, 1920
Armstrong, S. H. Mechanisms of Action of Serum Albumin Therapy in Internal Medicine. Am. J. Med. 4:390–397, 1948
Aschoff, L. Regeneration and Hypertrophy. Erg. d. allg. Path. u. path. Anat., 5:22–72, 1898
——— Lectures on Pathology. New York, Paul B. Hoeber, 1924.
——— Quoted by McMichael, 1934.
Asellius. De lactibus sive lacteis venis. Mediolane, 1627.
Ashburn, L. L., Endicott, K. M., Daft, F. S., and Lillie, R. D. The Non Portal Distribution of Trabeculae in Dietary Cirrhosis of Rats and Carbon Tetrachloride Cirrhosis in Rats and Guinea Pigs. Am. J. Path.,
———

Hepatectomy. II. Arch. Path., 53:209–216, 1951.
Aunap, E. The Course of the Hepatic Artery in the Liver. Jahrb. f. morph. u. mikrosk. Anat. Part 2, Ztschr. f. Mikrosk., anat. Forsch., 25:238–250, 1951
Baer, R
Baillie, M
Bambri
1905
——— and Leathes, J. B. The Effect of Arterial or Venous Obstruction upon the Nutrition of the Liver Cells. Biochem. J., 2:25–33, 1907.
——— and Trevan, J. W. Some Actions of Adrenalin upon the Liver. J. Physiol., 51:460–468, 1917.
Banti, G. Banti's Disease. Translation from Italian by Robert-Tissot. Folio Haemat., 10:33–71, 1910
——— Splenic Anemia. Arch. d. scuola d'anat. path., Firenze, 2:55–121,

C Thomas, 1945
Barcroft, J., and Shore, L. E. The Gaseous Metabolism of the Liver. I. J
Baronol
Resection in its Treatment. Surgery, 25:135–163, 1949
——— and Wangensteen, O. H. Obstruction of Splenic Vein Increases Weight of Stomach and Predisposes to Erosion or Ulcer. Proc. Soc. Exper. Biol. & Med., 59:234–238, 1945

Bartlett, F. K, Corper, H J, and Long, E R The Independence of the Lobes of the Liver. Am J Physiol, 35 36–50, 1914

Bateman, J C, Shorr, H M, and Elgvin, T Hypervolemic Anemia in Cirrhosis J Clin Investigation, 28 539–546, 1949

Baudouin, M The Ligature of the Hepatic Artery Ann internat de chir gastro-intest, 3 39–42, 1909

Bauer, A In the Intrahepatic Venous Circulation Arch de méd exper et d'anat path, 22 1–16 1910

Bauer, W, Dale, H H, Poulsson, L T, and Richards, D W The Control of Circulation through the Liver J Physiol, 74 343–375, 1932

Baxter, J H, and Ashworth, C T Renal Lesions in Portal Cirrhosis Arch Path, 41 476–488, 1946

Bayliss, W M, and Starling, E H Observations on Venous Pressures and Their Relationship to Capillary Pressures J Physiol, 16 159–202, 1894.

Beale, L S The Liver London, J and A Churchill, 1889

——— On Some Points in the Anatomy of the Liver of Man and Vertebrate Animals London, J Churchill, 1856

——— On the Lymphatics of the Liver Arch Med, 1 113–115, 1858

Bean, W B, Franklin, M, Embick, J F and Daum K Absorption Studies Using Portal Anastomotic Veins J Clin Investigation, 30 263–273, 1951

Bearn, A G, Billing, B, and Sherlock S The Effect of Adrenaline and Noradrenaline on Hepatic Blood Flow and Splanchnic Carbohydrate Metabolism in Man J Physiol, 115 430–440, 1951

Beattie, A S, and Hildebrand, E Thrombosis of the Hepatic Veins Arch Path 50 247–254, 1950

Beck, J S P, and Berg, B N The Circulatory Pattern in the Islands of

Am J

d in the

Perfusion of Living Organs and Tissues Artificial Solutions Substituted for Blood Serum and the Resulting Injury to Parenchymal Cells Am J Physiol, 52 101–119, 1920

Benz, E J, Baggenstoss, A H and Wollaeger, E E Atrophy of the Left Lobe of the Liver Arch Path 53 315–330 1952

Berg, B N A Study of the Islands of Langerhans in Vivo with Observations on the Circulation Am J Physiol, 95 186–189 1930

Liver Compt rend Acad de sc, 84 1201–1207, 1877

——— Veins Establishing a Direct Communication between the Portal Vein and the Inferior Vena Cava Compt rend Soc de biol, 1 87, 1849

Bernstein, S. S., Echinococcus Cyst of the Liver. Prolonged Course with Operative Removal and Complicating Thrombosis of Portal Vein. J Mt Sinai Hosp 8 399–408 1941–2

Decompensated Hepatic Cirrhosis J. Lab & Clin. Med. *40* 777–778, 1952

Betz, W The Circulation within the Liver, Especially that of the Hepatic Artery Ztschr. f rat. Med., *18*.44–60, 1863.

Bichat, M F X · Anatomie Générale, appliqué à la physiologie et à la médi-

Studies of Intestinal Absorption of Glucose Using Abdominal Collateral Veins Bull Johns Hopkins Hosp 85·183–199 1949.

Blain, A . Surg, Gynec.

——— e Operation of Choice in Selected Cases of Portal Hypertension and Banti's Syndrome Ann Surg, *131* 92–98, 1950.

Blakemore, A H Portacaval Anastomosis· A Report of Fourteen Cases. Bull. N Y. Acad Med, *22* 254–264, 1946.

——— Indications for Portacaval Anastomosis Surg, Gynec. & Obst, *84*. 645–653, 1947

——— The Portacaval Shunt in the Surgical Treatment of Portal Hypertension Ann Surg, *128* 825–841, 1948

———

———

———

13, 1952

——— Portacaval Shunting for Portal Hypertension. Surg, Gynec. & Obst, *94* 443–454, 1952

——— and Fitzpatrick, H F The Surgical Management of the Postsplenectomy Bleeder with Extrahepatic Portal Hypertension Ann Surg, *134*· 420–432, 1951.

——— and Lord, J W, Jr A Non-Suture Method of Blood Vessel Anastomosis Ann Surg, *121* 435–451, 1945

——— and Lord, J W, Jr The Technique of Using Vitalium Tubes in Establishing Portacaval Shunts for Portal Hypertension. Ann. Surg, *122* 476–488, 1945.

Blalock, A The Use of Shunt or By-Pass Operations in the Treatment of Certain Circulatory Disorders Ann Surg, *125* 129–140, 1947.

Bloch See Knisely, 1945

Bloch, E. H Some Actions of Adrenalin Chloride and Acetyl-Beta-Methyl-Choline Chloride on Finer Vessels of Living Frog Liver Lobules Anat Rec, *76* Suppl, *76* 7, 1940.

Blondheim, S H, and Kunkel, H G · Portal Blood in Collateral Veins of

Patients with Cirrhosis Proc Soc Exper Biol & Med, 75 38–41, 1950.
Blondlot, N Essay on the Functions of the Liver Paris, V Masson, 1846
Bloom, H J G Venous Hums in Hepatic Cirrhosis Brit Heart J, 12 343–350, 1950
Bogoras, N On the Anastomosis of the Superior Mesenteric Vein to the Inferior Vena Cava in Cirrhosis of the Liver Munchen med
[illegible]
a In
[illegible] s, Jr
[illegible] Conf,
[illegible]
—— and Mann, F C [illegible] Ann Int Med, 5 699–711, 1931
—— and Mann, F C The Physiology of the Impaired Liver Ergebn Physiol, 38 445–492, 1936
Bolté, R Anomalies of the Hepatic Artery J de l'Hôtel-Dieu de Montreal, 8 309–313, 1939
Bolton, C An Experimental Study of the Pathology of Cardiac Dropsy and Its Relation to that of Local Venous Obstruction J Path & Bact, 14 49–88, 1910
—— The Pathological Changes in the Liver Resulting from Passive Venous Congestion Experimentally Produced J Path & Bact, 19 258–264, 1915
—— and Barnard, W G The Pathological Occurrences in the Liver in Experimental Venous Stagnation J Path & Bact, 34 701–709, 1931
Bongiovanni, A M, and Eisenmenger W J Adrenal Cortical Metabolism in Chronic Liver Disease J Clin Endocrinol, 11 152–171, 1951
Borst, J C G The Maintenance of an Adequate Cardiac Output by the Regulation of the Urinary Excretion of Water and Sodium Chloride Acta med Scandinav, Suppl 207 1–71 1948
Botkin, S P The Contractility of the Spleen and the Effect of Infective Processes on the Spleen, Liver, Kidneys and Heart Berlin, A Hirschwald, 1874
Boyce, F F The Role of the Liver in Surgery Springfield Ill, Charles C Thomas, 1941
——, Lampert, R, and McFetridge E M Occlusion of the Portal Vein An Experimental Study with its Clinical Application J Lab & Clin
[illegible]
Disease New England J Med, 240 456–461, 1949
——, *Ingelfinger, F J, and Bradley, G P Hepatic Circulation in Cirrhosis* of the Liver Circulation, 5 419–429 1952
——, Ingelfinger, F J, Bradley, G P, and Curry, J J The Estimation of Hepatic Blood Flow in Man J Clin Investigation 24 890–897 1945
Brandes, W W The Effect of Mechanical Constriction of the Hepatic Veins Arch Int Med, 44 676–692 1929
Brendle, E On the Structure of the Human Portal Vein and its Radicals Acta anat 10 108–128, 1950

of Biliary Origin Arch de physiol. norm. et path., 3.345–365, 444–454 1884

. Philosoph

, 1901.

Course of the Hepatic Artery and

1940

d Duodenum for Carcinoma. Surg Gynec & Obst , 65 681–684, 1937.

——— Pancreaticoduodenectomy A "Curative" Operation for Malignant

———

1094–1100, 1941

———, Bigelow, R. R., and Nichols, S.. Elective Occlusion and Excision of the Portal Veins Surgery, *17*.781–785, 1945.

Budd, G On Diseases of the Liver London, G J. Palmer, 1845; Berlin, Von Henoch, 1846, Philadelphia, Lea & Blanchard, 1846, 1857.

——— Disease of the Liver Lancet, *1*.654–656, 1850

——— Cirrhosis. Med Times, London, 2 251–253, 1851.

Burdenko, N The Question of Ligation of the Portal Vein. Deutsche Ztschr f Chir, *124* 95–112, 1913

Burow, K A Contribution to the Study of the Fetal Veins. Arch. f Anat. Physiol u wissensch Med , 1838, pp. 44–45.

Burton-Opitz, R On the Flow of Blood in the Region of the Portal Vein The Volume of Blood Flow in the Splenic Vein. Pfluger's Arch f. d ges Physiol , *129* 189–216, 1909

——— The Vascularity of the Liver. I Flow of the Blood in the Hepatic Artery Quart J Exper Physiol , 3 297–313, 1910

——— The Vascularity of the Liver III The Effect of Stimulation of Single Nerves of the Hepatic Plexus upon the Flow in the Hepatic Artery Quart J Exper Physiol , 4 103–112, 1911.

——— The Vascularity of the Liver IV The Magnitude of the Portal Inflow Quart J Exper Physiol , 4 113–125, 1911.

——— The Vascularity of the Liver. V. The Influence of the Greater Splanchnic Nerves upon the Arterial Inflow Quart J. Exper. Physiol , 4 82–90, 1912

———

———

———

———

334, 1915

Butler, H Some Derivatives of the Foregut Venous Plexus of the Albino Rat with Reference to Man J Anat , *86* 95–109, 1952.

Cain, J C , Grindlay, J H , Bollman, J. L , Flock, E V , and Mann, F C·

Lymph from Liver and Thoracic Duct An Experimental Study Surg, Gynec & Obst, 85 559–562, 1947
Cameron, G R Liver Regeneration and Biliary Obstruction J Path & Bact, 41 283–287, 1915
——— and De Sarum, G S W A Method for Permanently Dissociating the Spleen from the Portal Circulation (the Marsupialized Spleen) J Path & Bact, 48 41, 1939
——— and Karunaratne, W A F Carbon Tetrachloride Cirrhosis in Relation to Liver Regeneration J Path & Bact, 42 1–19, 1936
———, Karunaratne, W A F, and Thomas, J C Massive Necrosis ("Toxic Infarction") of the Liver Following Intra-Portal Administration of Poisons J Path & Bact, 44 297–303, 1937
——— and Mayes, B T Ligation of the Hepatic Artery J Path & Bact, 33 799–828, 1930
Caputi, A P, and Warthin, T. A Chiari's Disease Hepatic Vein Thrombosis New England J Med, 246 1004–1006, 1952
Carswell, R Pathological Anatomy Illustrations of the Elementary Forms of Disease London, Longman, Orme, Brown Green & Longman, 1838
Cates, H B Surgical Treatment for Cirrhosis Progress Subsequent to Omentopexy Arch Int Med, 71 183–205, 1943
Cauchois, A Chronic Splenomegaly Originating in Pylothrombosis Paris Thesis, G Steinheil, 1908
Caughy, J L Quoted by Rousselot J A M A, 1936
Cavalcanti, E M The Participation of the Superior Mesenteric Artery in the Hepatic Blood Supply Rev brasil de cir, 22 267–276, 1951
Chalmers, T C, and Davidson, C S A Survey of Recent Therapeutic Measures in Cirrhosis of the Liver New England J Med, 240 449–454 1949
Charcot, J M Of Common Cirrhosis Progrés méd, Paris, 4 668–669, 679–680 690–691, 703–704, 715–718, 1876
——— Diseases of the Liver In Complete Works Paris, Aux bureaux du progrés médical, 1888, vol 6, pp 1–253
Charkravarti, M and Tripod, J The Action in the Perfused Liver of Acetylcholine, Sympathomimetic Substances and Local Anaesthetics J Physiol, 97 316–328 1940
Charpy, A The Vena Cava Inferior The Vena Porta In Traité d'anatomie humaine, ed by P Poirier Paris, Masson, vol 2, pp 987–991, 997–1020
Chau, A Y S, Goldbloom, V, and Gurd, F N Clostridial Infection as a Cause of Death after Ligation of the Hepatic Artery Arch Surg, 63 390–402, 1951

Anat u z allg Path, 26 1–17, 1899
Child, C G III Pancreaticoduodenectomy and Other Problems Associated with the Surgical Management of Carcinoma Involving the Head of the Pancreas Ann Surg, 119 845–855, 1944
——— Radical One Stage Pancreaticoduodenectomy Surgery, 23 492–500, 1948
——— Advances in the Management of Pancreaticoduodenal Cancers In

Advances in Surgery Ed by W. D. Andrus. New York, Interscience Publishers, 1950, Vol. 2, pp. 495–561.

Child, C G, III Eck's Fistula Surg, Gynec. & Obst, 96:373–376, 1953.

——— Reconstruction of the Gastrointestinal, Biliary and Pancreatic Systems Following Pancreaticoduodenectomy. In Treatment of Cancer and Allied Diseases Ed. by G. R. Pack & I. M Ariel. New York, Paul B Hoeber, in press.

——— Ligation of Portal Radicals in Puppies Unpublished Data.

——— and Ellis, J Radical Pancreaticoduodenectomy. Report of Two Autopsies Performed Four and Five Years after Operation. Ann Surg, *132* 80–87, 1951

——— and O'Neill, E. A Palliative Surgical Procedures for the Relief of Biliary and Pancreatic Obstruction due to Cancer In Treatment of Cancer and Allied Diseases Ed. by G R. Pack & I. M. Ariel. New York, Paul B. Hoeber, in press

——— and Payne, M A Portal Hypertension In. Monographs in Medicine Ed by W B Bean Baltimore, Williams & Wilkins Co, 1952, pp. 132–171

———, Barr, D, Holswade, G R., and Harrison, C S: Liver Regeneration Preliminary Report Proc Soc. Exper Biol. & Med, *82* 283–285, 1953 Also Ann Surg, *138* 600, 1953

———, Hays, D M, and McClure, R D, Jr · Studies of the Hepatic Circulation in the *Macaca mulatta* Monkey and in Man. Surg Forum, Am. Coll Surgeons, 1951 Philadelphia, W. B Saunders Co, 1952, pp 140–146

———, Holswade, G R, McClure, R D, Jr, Gore, A L, and O'Neill, E A Pancreaticoduodenectomy with Resection of the Portal Vein in the *Macaca mulatta* Monkey and in Man. Surg, Gynec & Obst, *94*: 31–45, 1952

———, Milnes, R F, Holswade, G R, and Gore, A. L Sudden and Complete Occlusion of the Portal Vein in the *Macaca mulatta* Monkey. Ann Surg, *132* 475–495, 1950

Chrzonszczewsky, N The Anatomy and Pathology of the Liver. Virchow's Arch f path Anat, *35* 153–164, 1866

Clark, G A A Comparison of the Effects of Adrenalin and Pituitrin on the Portal Circulation J Physiol, *66* 274–279, 1928

Clinicopathological Conferences North Carolina M. J, *11*·359–364, 1950.

Cohn, R, and Herrod, C Some Effects upon the Liver of Complete Arterial-

Arch f path Anat, *67* 153–165, 1876

Colmers, F Intrahepatic Aneurism and Gall Bladder Fistula after Rupture of the Liver [illegible] c Artery Beitr klin Ch [illegible]

Colp, R The Treat [illegible] With a Report of Thr [illegible], Gynec & O [illegible]

Copher, G [illegible] Ven [illegible] Surg, 17.408–419, 1928

onsecutive Cases Ann

Veins

Arch

. Eng-

2 Ed,

Their Relation to Muscarine J Pharmacol & Exper Therap, 6 147–190, 1914

——— I Intro

——— II Local 129

——— 28 1493–1495, 1935

——— and Laidlaw, P

Dallas and Phemister

Daniel, P M, and Pric

Nerves and of Adrenalin upon the Circulation of the Portal Venous Blood within the Liver J Physiol, 114 538–546, 1951

——— and Prichard, M M

Venous Blood Flow J

——— and Prichard, M M

Venous Blood within the Liver J Physiol 114 521–537, 1951

——— Prichard, M M L, and Reynell P C The Portal Circulation in Experimental Cirrhosis of the Liver J Path & Bact, 64 53–60, 1952

——— Prichard, M M L, and Reynell, P C The Portal Circulation in Rats with Liver Cell Damage J Path & Bact, 64 61–64, 1952

Davidson, C S, Gibbons, T B and Faloon W W Systemic and Portal Venous Pressures in Cirrhosis of the Liver J Lab & Clin Med 35

Ann West Med

duced Blood Flow

Dist 69 360–361 1949

Davis, N C, Hall, C C, and Whipple G N The Rapid Construction of Liver Cell Protein on a Strict Carbohydrate Diet Contrasted with Fasting III Mechanism of Protein-Sparing Action of Carbohydrate Arch Int Med 23 689–710 1919

——— and Whipple, G. H Liver Regeneration Following Chloroform Injury as Influenced by the Feeding of Casein or Gelatin Arch Int Med., 27 679–687, 1921

——— and Whipple, G H Liver Regeneration Following Chloroform Injury as Influenced by Various Diets Arch Int Med, 23 711–722, 1919

Davison, A. Mammalian Anatomy 7th Ed Philadelphia, The Blakiston Co 1947.

Advances in Surgery Ed by W D Andrus. New York, Interscience Publishers, 1950, Vol 2, pp 495–561.

Child, C G, III Eck's Fistula Surg, Gynec. & Obst, 96.373–376, 1953.

——— Reconstruction of the Gastrointestinal, Biliary and Pancreatic Systems Following Pancreaticoduodenectomy. In Treatment of Cancer and Allied Diseases Ed by G R. Pack & I. M. Ariel. New York, Paul B Hoeber, in press

——— [illegible] ed Data.

——— [illegible] Report of Two [illegible] Operation Ann. Surg, 132 80–87, 1951

——— and O'Neill, E A Palliative Surgical Procedures for the Relief of Biliary and Pancreatic Obstruction due to Cancer. In. Treatment of Cancer and Allied Diseases Ed by G R. Pack & I. M Ariel. New York, Paul B Hoeber, in press

——— and Payne, M A Portal Hypertension. In Monographs in Medicine Ed by W. B Bean Baltimore, Williams & Wilkins Co, 1952, pp 132–171

———, Barr, D, Holswade, G R, and Harrison, C. S: Liver Regeneration Preliminary Report. Proc. Soc Exper. Biol. & Med, 82 283–285, 1953 Also Ann Surg, 138 600, 1953.

———, Hays, D M, and McClure, R D, Jr · Studies of the Hepatic Circulation in the *Macaca mulatta* Monkey and in Man. Surg Forum, Am. Coll Surgeons, 1951. Philadelphia, W. B. Saunders Co, 1952, pp 140–146

———, Holswade, G R, McClure, R D., Jr, Gore, A L., and O'Neill, E A Pancreaticoduodenectomy with Resection of the Portal Vein in the *Macaca mulatta* Monkey and in Man. Surg, Gynec & Obst, 94 31–45, 1952

———, Milnes, R F, Holswade, G R, and Gore, A L Sudden and Complete Occlusion of the Portal Vein in the *Macaca mulatta* Monkey. Ann Surg, 132 475–495, 1950

Chrzonszczewsky, N The Anatomy and Pathology of the Liver. Virchow's Arch f path Anat, 35 153–164, 1866

Clark, G A. A Comparison of the Effects of Adrenalin and Pituitrin on the Portal Circulation J Physiol, 66 274–279, 1928

Clinicopathological Conferences North Carolina M. J, 11·359–364, 1950

Cohn, R, and Herrod, C Some Effects upon the Liver of Complete Arterial-[illegible]

[illegible] Arch f path Anat, 67 153–165, 1876.

Colmers, F Intrahepatic Aneurism and Gall Bladder Fistula after Rupture of the Liver Hea[illegible] e Artery. Beitr klin Chir, [illegible]

Colp, R The Treatment [illegible] With a Report of Three Cases of Ligation of the [illegible], Gynec & Obst, 43 627–645, 1926

Copher, G H, and Dick, B M "Stream Line" Phenomena in the Portal Vein and the Selective Distribution of Portal Blood in the Liver Arch Surg, 17 408–419, 1928.

Meta-Silicate) Administered Intravenously to Cats and to Rabbits J Exper Med, 37 829–850, 1923
Drummond, D, and Morison, R A Case of Ascites Due to Liver Cirrhosis Cured by Operation Brit M J, 2 728–729, 1896
Dunlap, R W, Jr, Hollenbeck, G A, and Hanlon, D G Portal Hypertension Associated with Sarcoidosis and with Hemochromatosis Proc Staff Meet, Mayo Clin, 27 266–272, 1952
Dwight, R W, and Ratcliffe, J W Aneurism of the Hepatic Artery Report of a Case Treated by Wiring Surgery, 31 915–920, 1952
Dye, W S, Bennett, H, Baker, L, and Julian, O C Observations on Inconstancy of Portal Hypertension in Hepatic Cirrhosis Surg Forum, Am Coll Surgeons, 1952 Philadelphia, W B Saunders Co, 1953
Eaton, T H Comparative Anatomy of the Vertebrates New York, Harper & Brothers, 1951
Eck, N V On the Question of Ligature of the Portal Vein Voyenno-med, 130 1–2, 1877 Translation Surg, Gynec & Obst, 96 375–376, 1952
Eckhart, P Blood Volume and Circulation of the Liver Following Splanchnectomy Pflüger's Arch f d ges Physiol 236 361–366, 1935
Edens, E Thrombosis of the Splenic and Portal Veins and Banti's Disease Mitt a d Grenzgeb d Med u Chir, 18 59–78, 1908
Edmunds, C W Some Vasomotor Reactions of the Liver J Pharmacol & Exper Therap, 6 569–590, 1915
Edwards, E A Clinical Anatomy of the Lesser Varieties of the Inferior Vena Cava Angiology, 2 85–99, 1951
——— Functional Anatomy of the Porta-Systemic Communications Arch Int Med, 88 137–154, 1951
Effler, D B, Greer, A E, and Sifers, E C Anomaly of the Vena Cava Inferior Report of Fatality after Ligation J A M A, 146 1321–1322, 1951
Egbert, H L, and Raber, R M The Physiologic Effect of Hepatic Artery and Portal Vein Ligation Surgical Forum, American College of Surgeons, 1951 Philadelphia, W B Saunders Co, 1952, pp 153–157
Eisenmenger, W J Role of Sodium in the Formation and Control of Ascites in Patients with Cirrhosis Ann Int Med, 37 261, 1952
———, Ahrens, E H, Jr, Blondheim, S H and Kunkel, H G The Effect of Rigid Sodium Restriction in Patients with Cirrhosis of the Liver and Ascites J Lab & Clin Med, 34 1029–1038, 1949
———, Blondheim, S H, Bongiovanni, A M, and Kunkel, H G Electrolyte Studies on Patients with Cirrhosis of the Liver J Clin Investigation, 29 1491–1499, 1950
Elias, H The Liver Cord Concept after 100 Years Science, 110 470–472, 1949
——— A Re-Examination of the Structure of the Mammalian Liver I Parenchymal Architecture Am J Anat, 84 311–327, 1949
——— A Re Examination of the Structure of the Mammalian Liver II The Hepatic Lobule and its Relation to the Vascular and Biliary Systems Am J Anat 85 379–426, 1949
——— Morphology of the Liver In Liver Injury Trans 11th Conf., April 30–May 1 1952 Josiah Macy, Jr Foundation, 1953, pp 111–196.
——— and Bengelsdorf, H The Structure of the Liver of Vertebrates. Acta anat Scandinav 14 297–337, 1952

Dawes, G S The Vaso-Dilator Action of Potassium. *J. Physiol*, 99.224–238, 1941

De Britto, R, Vaz, O, Abdalla, P, and Da Silva, R Renogastroepiploic Anastomosis in the Treatment of Portal Hypertension. *Surgery*, 31. 502–510, 1952.

Delorme, E J. Arterial Perfusion of the Liver in Shock. *Lancet*, 1 259–263, 1951

De Martel, M F Brief Summary of the Technique of Eck Operation. Rev de chir, Paris, 42 1181, 1910.

De An

Dey ner as Determined by Drug Actions and Vascular Injections. Am J. Physiol, 132 713–724, 1941.

Diemerbroeck, I de The Anatomy of Human Bodies Comprehending the Most Modern Discoveries and Curiosities in the Art. Translated by William Salmon Little Britain, W. W. Whitwood, 1694.

Disse, J The Lymphatics of the Mammalian Liver. Arch. f. mikrosk. Anat, 36 203–222, 1890.

Divine, J Lieno-Renal Anastomosis for Cirrhosis of the Liver and Ascites M J Australia, 1 14–15, 1948

Divine, J, Jr. Personal Communication

Dochios, M, and Dreifus, L S · Antidiuretic Hormone Studies in Patients Presenting Edema Am J M Sc., 222.538–542, 1951.

Dock, W Role of Increased Hepatic Arterial Flow in Portal Hypertension of Cirrhosis Tr A Am Physicians, 57:302–305, 1942.

Doggett, T H The Capillary System of the Dog's Spleen. Anat. Rec, 110· 65 76 1951

Dohan, G C, Richardson, E M, Bluemle, L. W., Jr., and Gyorgy, P · Hormone Excretion in Liver Disease. J Clin. Investigation, 31 481, 1952.

Dotter, C T, Payne, M A, and O'Sullivan, W Catheterization of the Portal Vein in Man Following Porta-Caval Anastomosis. Ann. Surg, 132 310–311, 1950

Douglass, B E, Baggenstoss, A H, and Hollinshead, W. H: The Anatomy of the Portal Vein and Its Tributaries Surg, Gynec & Obst, 91.562–575, 1950

———, Baggenstc System of

———and Snell, on Modern Methods of Treatment Gastroenterology. 15 407–424, 1950

Drill, V A, and Frame, B Antidiuretic Activity of Liver Extracts and of Urine from Patients with Hepatic Cirrhosis Federation Proc., 7 215 1948.

Drinker, C K Extravascular Protein and the Lymphatic System. Ann N. Y Acad Sc, 46 807–822, 1946.

——— and Shaw, L A Quantitative Distribution of Particulate Matter (Manganese Dioxide) *Administered Intravenously in the Cat* J Exper Med, 33.77–97, 1921.

———, Shaw, L A, and Drinker, K. R. The Deposition and Subsequent Course of Particulate Matter (Manganese Dioxide and Manganese

Faloon, W W, Eckhardt, R D, Murphy, T. L, Cooper, A M, and Davidson, C S An Evaluation of Human Serum Albumin in the Treatment of Cirrhosis of the Liver J Clin Investigation, 28 583–593, 1949

Falor, W H, and Golings, R H Right Thoracoabdominal Approach for Portacaval Anastomosis Arch Surg, 62 499–505, 1951.

Fantus, B, and Seed, L The Therapy of Cook County Hospital The Therapy of Acute Peripheral Circulation Failure J A M A, 114 2010–2015 1940

Farnsw

———

Various Origins. Qualitative and Quantitative Definition of Cations and Anions in Hepatic Cirrhosis J Lab & Clin Med, 33 1545–1553

Kidneys and Liver Hist et Mém de l'Acad Roy des Sciences, 1749, pp 489–530

Fine, J Recent Advances in Traumatic Shock In Advances in Surgery Ed by W D Andrus New York, Interscience Publishers, 1949, Vol 1, pp 1–64

———, Frank, H Schweinburg, F, Jacob, S, and Gordon, T The Bacterial Factor in Traumatic Shock Ann New York Acad Sc, 55 429–437, 1952

———, Seligman, A M, and Frank, H A Traumatic Shock An Experimental Study Including Evidence Against the Capillary Leakage Hypothesis Ann Surg, 118 238–254, 1943

———, Seligman, A M, and Frank, H A On the Specific Role of the Liver in Hemorrhagic Shock Ann Surg, 126 1002–1009, 1947

Fishback, F C A Morphologic Study of Regeneration of Liver after Partial Removal Arch Path, 7 955–977, 1929

Fischler F Meat Intoxication in Animals with Eck Fistulas Deutsch Arch f klin Med, 104 300–320, 1911

——— and Schroder, R A Simple Manner of Executing the Eck Fistula Arch f exper Path u Pharmak, 61 428–433, 1909

Fishback, F C A Morphologic Study of Regeneration of the Liver Arch Path, 7 955–977, 1929

Fisher, B, Zerbe, J W, and Vars, H M Effect of Partial Hepatectomy, Protein Realimentation, and Bile Refeeding on Biliary Secretion in the Rat Surgical Forum, American College of Surgeons, 1952. Philadelphia, W B Saunders Co, 1953

Foa, P Hematopoiesis Arch per le sc med, 5 366–383, 1882

——— and Salvioli, G Anatomical and Experimental Investigation of the Pathology of the Liver Arch per le sc med, 2 1–25, 225–244, 1878

Foot, N C The Reticulum of the Human Spleen Anat Rec, 36 79–90, 1927

——— Endothelium of Venous Sinuses of the Human Spleen Anat Rec, 36 91–101 1927

François Franck, C A and Hallion, L Studies on the Motor Innervation of the Liver Arch de physiol norm et path, 9 434–447, 1897

Frank, H A, Glotzen, P, Jacob, S W, and Fine, J Traumatic Shock. XIX

El

El

Portal Obstruction Proc Soc Exper. Biol. & Med, 29 1122-1123, 1932

——— and Cole, W. H Hemorrhage and Shock as Causes of Death Following Acute Portal Obstruction Arch. Surg, 28 1166-1175, 1934.

——— and Lieberman, Z H The Pancreas Contributions of Clinical Interest in 1950 Gastroenterology, 21:24-50, 1952.

Emmerich, C Cavernomatous Transformation of the Portal Vein. Frankfurt Ztschr f Path 10 362-373, 1912.

Enderlen, Holtz and Magnus-Alsleben The Pathology and Therapy of Portal Obstruction Investigations on the Eck Fistula Ztschr. f d. ges. exper Med, 3 223-302, 1914

Eppinger, H The Pathology of the Circulatory Correlations In Handbuch norm u path Physiol Ed by Bethe Bergman. Berlin, J. Springer, 1931

——— and

der k

Eppinger, F

1922

Epstein, F H, Lesser, G T, and Berger, E Y. Renal Function in Decompensated Cirrhosis of the Liver Proc Soc. Exper. Biol & Med, 75. 822-824, 1950

Essex, H E, and Thomas, W D The Response of the Hepatic Venous Circulation to Certain Substances Given Intravenously. Proc. Staff Meet, Mayo Clin, 25 34-36, 1951.

Evans,

Everson

Surgical Forum, American College of Surgeons, 1951. Philadelphia, W B Saunders Co, 1952

——— and Cole, W H Ligation of Splenic Artery in Patients with Portal Hypertension Arch Surg, 56 153-160, 1948.

Exler Autoserotherapy in Tuberculosis of the Peritoneum by Continuous Drainage of Ascitic Fluid under the Skin. Med. Klin, 6 627-628. 1910 Also Verh Anal d deutsch, Gesellsch. f. Chir, 39:257-258, 1910

Fabricius ad Aquapendente, H The Embryological Treatises of Fabricius of Aquapendente Facsimile edition Ithaca, Cornell University Press, 1942

Falkenberg, J Contribution to Knowledge Concerning Chronic Constrictions of the Portal Vein Virchows Arch f path Anat, 268 769-791, 1928

Faloon,

Investigation, 28 595-602, 1949

Géraudel, E Cardiac Liver Fragile and Resistant Zones Bull Soc anat de Paris, *80* 85, 1905
——— Note on the Structure of the Liver Compt rend Soc de biol *58*. 468–470, 1905.
——— Notes on the Lymphatics of the Liver Bull et mem Soc Anat de Paris, *82* 159–161, 1907
——— The Cardiac Liver Response to Mr Bauer Presse méd, *15* 761–762, 1907
Gerber, I E, and Mendlowitz, M Visceral Thrombophlebitis Migrans Ann Int Med *30* 560–578, 1949

Fistulas and Arterial Aneurisms Surgery, *32* 259–274, 1952
Gerlach, J Contribution to the Study of the Structure of the Liver Mainz, 1849
Gerlach, W Disturbances
path Anat u Histol
Ghiron, V, and Badalla, L
with the Hepatic Artery Policlinico (sez chir), *40*·308–318, 1933
——— and Brunacci, A Ligature of the Hepatic Artery and Anastomosis of Its Peripheral End with the Portal Vein Boll e atti accad med, Roma, *55* 60–62, 1929
Gilbert, A and Villaret, M
Portal Hypertension
——— and Villaret, M On
Circulation Compt Rend Soc de biol, *61* 481–483, 1906
——— *and Weil, E On the Tension of the Fluids of Ascites Compt Rend*
in and Its Main Branches
Vein J méd, Bordeaux, 1843.
——— Observations and Investigations on Obliteration of the Portal Vein J méd, Bordeaux, *1* 61–132 1856 Rev in J d'anat, et de physiol norm et path *1* 562, 1864
Glauser, Frank Studies on Intrahepatic Arterial Circulation Surgery, *33* 333, 1953
——— Anatomia hepatis London Du Gardianis, 1654 Amsterdam J Ravestein, 1659
——— Tractus de ventriculo et intestines Amsterdam, Jacobum Juniorum, 1677
Glotzer,

Glynn
Liver Injury by Carbon Tetrachloride Clin Sc 6 235–240 1948
——— Himsworth H P, and Lindan O The Experimental Production and Development of Diffuse Hepatic Fibrosis ('Portal Cirrhosis") Brit J Exper Path 29 1–9 1948
Goldblatt, H Cirrhosis Report of Pathologists on Cirrhosis Study In: Liver Injury Trans Sixth Conf, May 1–2, 1947 Josiah Macy, Jr Foundation, 1948, *pp* 9–12

Hemorrhagic Shock in Eck-Fistula Dogs. Am. J Physiol, *167*:508–512, 1951

Frank, H A, Seligman, A M, and Fine, J.: Traumatic Shock. XIII The Prevention of Irreversibility in Hemorrhagic Shock by Vivi Perfusion of the Liver J Clin Investig, *25* 22–29, 1946.

Franke, E A Case of the Talma Operation Verhandl d. deutsch Gesellsch f Chir, *31* 101–103, 1902.

——— Experimental Investigation of the Anastomoses of the Portal Circulation Verhandl. d deutsch Gesellsch. f. Chir, *40* 267–271, 1911

——— An Experimental Study on Continuous Drainage in Ascites Verhandl d deutsch Gesellsch. f. Chir, *42* pt. 2, 215–230, 1912

——— The End-to-Side Anastomosis of the Portal Vein and the Inferior Vena Cava as Substitute for the Eck Fistula Ztschr. f. biol. Technik u Methodik, 2 262–271, 1912

Franklin, K J. A Monograph on Veins Springfield, Ill, Charles C Thomas. 1937.

Franklin, M, Bean, W B, Paul, W D., Routh, J I., De La Huerga, J, and Popper, H Electrophoretic Studies in Liver Disease. J. Clin. Investigation, *30* 729–738, 1951

Fraser, D, Rappaport, A M, Vuylsteke, C A, and Colwell, A. R, Jr · Effects of the Ligation of the Hepatic Artery in Dogs Surgery, *30* 624–641, 1951

Fraser, F C, and Fainstat, T D The Production of Congenital Defects in the Offspring of Pregnant Mice Treated with Cortisone. Pediatrics, *8* 527–533, 1951

———, Fainstat, T D, and Kalter, H: Experimental Production of Congenital Defects, with Particular Reference to Cleft Palate Surgical Forum, Proc American College of Surgeons, Sept. 23–25, 1952

Fraser, J, and Brown, A K A Clinical Syndrome Associated with a Rare Anomaly of the Vena Porta System. Surg., Gynec. & Obst, *78*.520–524, 1944

Frerichs, F T Atlas of the Liver Braunschweig, F. Vieweg, 1858–61

——— Clinical Treatise on Diseases of the Liver. New York, William Wood 1879.

Friedge [illegible] W · Role of Adrenal Cortex in [illegible] 53:354–363, 1950.

Friedm [illegible]: Portal Circulation in Experi[illegible], *134* 70–79, 1951.

Gabuzd [illegible] rsible Toxic [illegible] ven Cation [illegible] 952

Gad, J Studies on the Relations of the Blood Stream of the Portal Vein to the Blood Stream in the Hepatic Artery Dissertation, Berlin, G Schade, 1873

Galen De usu partium corporis humani. Lugduni, G Roullium, 1550.

Gardner, R E, Leeds, F H., and Freeman, N F Experimental Portacaval Anastomosis California Med, *69* 1–5, 1948

Garlock, J H, and Som, M L Further Observations in the Packing of Mediastinum for Esophageal Varices J. Thoracic Surg, *19* 572–580, 1950

Géraudel, E.: Anatomy and Physiology of the Cardiac Liver. Presse méd *12*:769–771, 1904.

Géraudel, E Cardiac Liver Fragile and Resistant Zones Bull Soc anat de Paris, 80 85, 1905
——— Note on the Structure of the Liver Compt rend Soc de biol 58 468–470, 1905
——— Notes on the Lymphatics of the Liver Bull et mém Soc Anat de Paris, 82 159–161, 1907
——— The Cardiac Liver Response to Mr Bauer Presse méd, 15 761–762, 1907
Gerber, I E, and Mendlowitz, M Visceral Thrombophlebitis Migrans Ann I
Gerbod

———

Gerlach
1849
Gerlach, W
path A
Ghiron, V, an
with the Hepatic Artery Policlinico (sez chir), 40 308–316, 1933
——— and Brunacci, A Ligature of the Hepatic Artery and Anastomosis of Its Peripheral End with the Portal Vein Boll e atti accad med, Roma, 55 60–62, 1929
Gilbert, A and Villaret, M Contribution to the Study of the Syndrome of Portal Hypertension Compt Rend Soc de biol, 60 820–823 1906
——— and Villaret, M On Certain Peculiarities of the Intrahepatic Venous
1906
Compt Rend

Main Branches

méd, Bordeaux,
1843
——— Observations and Investigations on Obliteration of the Portal Vein J méd, Bordeaux, I 61–132 1856 Rev in J d anat, et de physiol norm et path, I 562, 1864
Glauser, Frank Studies on Intrahepatic Arterial Circulation Surgery, 33 333, 1953
——— Anatomia hepatis London, Du Gardianis 1654 Amsterdam J Ravestein, 1659
——— Tractus de ventriculo et intestines Amsterdam, Jacobum Juniorum, 1677
Glotzer, D J, and Allen J G Effect of Intravenous Administration of Activated Human Plasma Euglobulin in Dogs Surgical Forum, Proc, American College of Surgeons, Sept 23–26 1952
Glynn L E, and Himsworth H P The Intralobular Circulation in Acute Liver Injury by Carbon Tetrachloride Clin Sc 6 235–240, 1948.
——— Himsworth, H P, and Landin, O The Experimental Production and Development of Diffuse Hepatic Fibrosis ("Portal Cirrhosis"). Brit J Exper Path, 29 1–9 1948
Goldblatt, H Cirrhosis Report of Pathologists on Cirrhosis Study. In Liver Injury Trans Sixth Conf, May 1–2, 1947 Josiah Macy, Jr Foundation, 1948, pp 9–12

Goldman, R Studies in Diurnal Variation of Water and Electrolyte Excretion. J Clin Investigation, 30 1191–1198, 1951
Gollwitzer-Meier, K Investigations on the Changes of the Venous Reflux Produced by Adrenalin Ztschr. f. d. ges. exper. Med, 69 367–376, 1930
——— Collapse of the Circulation Verhandl. d. deutsch. Gesellsch f. Kreislaufforsch, 11·15–33, 1938.
Goodyer, A V N, Relman, A S., Lawrason, F. D, and Epstein, F. H. Salt Retention in Cirrhosis of the Liver. J. Clin Investigation, 29 973–980, 1950
Gordon, E S, Chart, J J., and Meyer, E S · The Importance of a "Sodium Retaining Factor" in the Urine in the Mechanism of Edema Formation. J Clin Investigation, 31 633, 1952.
Gordon-Taylor, G A Rare Case of Severe Gastrointestinal Hemorrhage with a Note on Aneurism of the Hepatic Artery. Brit M. J, 1:504–505, 1943
Grab, W, Janssen, S, and Rein, H The Liver as Blood Depot. Klin Wchnschr, 8 1539, 1929.
Graham, R R, and Cannell, D Accidental Ligation of the Hepatic Artery Brit J Surg, 20 566–578, 1933
Grant, J L, Fitts, W T, Jr, and Ravdin, I S.· Aneurism of the Hepatic Artery Surg, Gynec & Obst, 91·527–531, 1950
Gray, H Anatomy of the Human Body Ed. by W. H. Lewis. 25th Ed

Gretsel· A Case of Splenic Anemia in a Child. Berl Klin Wchnschr, 3·212–214, 1866.
Griffith, F R, Jr, and Emery, F. E The Vasomotor Control of the Liver Circulation Am J Physiol, 95 20–34, 1930.
Grindlay, J H Discussion of Berman, Koenig, and Muller, 1951.
——— and Bollman, J L Regeneration of the Liver in the Dog after Partial Hepatectomy Role of the Venous Circulation Surg., Gynec & Obst, 94 491–496, 1952
——— Herrick, J F, and Mann, F C Measurement of the Blood Flow of the Liver Am J Physiol,
———, Mann, F C, and Bolln.
Blood Supply to the Norm
——— Thors, R, and Bollman,
ing the Liver on Hepatic
Dogs Surgical Forum, American College of Surgeons, 1952 Philadelphia, W B Saunders Co, 1953
Grinnell, R S Omentopexy in Portal Cirrhosis of the Liver with Ascites Ann Surg, 101 891–900, 1935
Grodins, F S, Osborne, S L., Ivy, A C, and Goldman, L · The Effect of Bile Acids on Hepatic Blood Flow Am. J Physiol, 132 375–388, 1941
Gross, A Traumatic Ulcers of the Stomach Mitt a d Grenz d Med u Chir, 10 713–725, 1902.
Gross, R E Coarctation of the Aorta Surgical Treatment of 100 Cases Circulation, 1 41–55, 1950.

Gross, R E, and Hufnagel, C A Coarctation of the Aorta Experimental Studies Regarding its Surgical Correction New England J Med, 233 287-293, 1945
Gruber, G B Beitraege zur Pathologie der dauernden Pfortaderverstopfung Arch f klin Med, 122 319, 1917
Gukke, N On the T[illegible] of the Eck Fistula Ztschr f exper Path u Ther, 3 706-7
Gurd, F N, Vars, H [illegible]
Liver after Partial [illegible]
Am J Physiol, 152 11-20, 1948
Haberer, H Experimental Ligation of the Hepatic Artery Arch f [illegible] Chir, 78 577-586, 1906
Habif, D V, Randall, H T, and Soroff, H S Surgery In press, 1953
Hahn, M, Massen, O, Nencki, M, and Pawlow, J The Eck Fistula between the Inferior Vena Cava and the Portal Vein and its Effect on the Organism Arch f exper Path u Pharmak, 32 161-210, 1893
Hall, C A, Frame, B, and Drill, V A Renal Excretion of Water and Anti diu[illegible] in Patients with Hepatic Cirrhosis and Rats with Die[illegible] 1949
Hallett, E [illegible] Blood
Fl[illegible]
Follow[illegible]
of Surgeons, 1951 Philadelphia,
———, Holton, G W, Paterson, J C, and Schilling, J [illegible]
Hepatic Glucose Production, and Splanchnic Oxygen Consumption in Normal Dogs and Following Eck Fistula Liver Blood Flow Before and After Splenectomy Surg, Gynec & Obst, 95 401-406, 1952
Hallopeau, P Lateral Suture of the *Portal Vein* Rev de chir, 42 141-161 1910
Handler, F B, Blache, J O, and Blumenthal, H T Comparison of Aging Processes in the Renal and Splenic Arteries in the Negro and White Races *Arch Path*, 53 29-53, 1952
Handley, W S The Surgery of the Lymphatic System Brit M J, 1 853-864, 922-928, 1910
Hanrahan, E M, Jr Splenic Anemia A Study of End-Results with and without Splenectomy Based on Thirty Five Cases Arch Surg, 10 639-642, 1925
Hara, K On the Effect of Splanchnicectomy on the Pressure and Circulatory Volume of the Portal Vein in the Cat Pfluger's Arch f d ges Physiol, 222 350-355, 1929
Harkins, H N Recent Advances in the Study and Management of Traumatic Shock Surgery, 29 231-294, 447-482, 607-624, 1941
Harper, H A, Gardner R E, Johansen, R, Galante, M, and McCorkle, H J Amino Acid Tolerance in Experimental Portacaval Anastomosis Surgery, 29 210-215, 1951
Hart, C On the Meaning of Sclerosis of the Portal Vein Arch f klin Chir, 116 337-360, 1921
Hartroft, W S Some Histological Aspects of Renal and Hepatic Acholuria paths In Liver Injury Trans Sixth Conf, May 1-2, 1947 Josiah Macy, Jr Foundation, 1948, pp 41-48
——— Accumulation of Fat in Liver Cells and in Lipodiastaemata Preceding Experimental Dietary Cirrhosis Anat Rec, 106 61-77, 1950.
——— The Locus of the Beginning of Dietary Cirrhosis In Liver Injury

Foundation,

Harvey, animalibus
Frankfort. Guilielmi Fitzeri, 1628 Facsimile, Paris, G. Dome, 1950. English Translation by C D Leake, Springfield, Ill, Charles C Thomas, 1928

Havens in Serum Albumin
Hepatic Cirrhosis

Hay, E B, and Webb, J K The Effect of Intravenous Sodium Dehydrochlorate on the Mortality Rate Following Hemorrhagic Shock. Surgery, 29 829–831, 1950

——— and Webb, J K The Effect of Increased Arterial Blood Flow to the Liver on the Mortality Rate Following Hemorrhagic Shock Surgery, 29 820–828, 1951

Hay, S H, and Wood, J E, Jr Cation Exchange Resins in the Treatment of Congestive Heart Failure Ann Int Med, 33 1139–1148, 1950.

Heidenhain, R, Editor Studies from the Physiological Institute of Breslau Leipzig, 1861–1868

——— Physiology of the Liver In Handbuch der Physiologie. Ed. by L. Hermann Leipzig, Vogel, 1883, Vol 5, pt 1.

——— Investigations and Problems in the Study of Lymph Formation. Pfluger's Arch f d ges Physiol, 49:209–301, 1891.

Heller, A Traumatic Thrombosis of the Portal Vein Verhandl d. deutsch. path Gesellsch, 7 182–189, 1904

Henle, F G H The Contractility of the Vessels Wchnschr ges. Heilk, 1840, pp 329–336

——— Handbook of the Blood Vessels of Man. Braunschweig, 1868 2nd Ed, 1882

——— Fundamentals of Human Anatomy. 2nd Ed Braunschweig, F Vieweg, 1883

Henle,

Henry,
York Med J, Feb 15, 1913

er Sitzungsb d k Akad d
96, 1866.

Arch f. mikr. Anat, 3 88–114, 1867

——— The Liver In Handbuch der Lehre von den Geweben Ed by S Strickler English translation, New York, William Wood, 1872, pp 407–427

Herrick, J B. Pericarditic Pseudocirrhosis of the Liver. Trans Chicago Path Soc, 5 71–82, 1902

Hering, P T, and Simpson, S The Lymphatics of the Liver Brit. M J, 2: 1797–1798, 1906

Hickman, J, Edwards, J E, and Mann, F C Venous Anomalies in a Dog Anat. Rec, 104:137–146, 1949

Higgins, G M, Mann, F C, and Priestley, J. T.. Experimental Pathology of

Arch

Higgin

Higgins,
214 436–441, 1947

Hiller, G L, Huffman, E R, and Levey, S Studies in Cirrhosis of the Liver J Clin Investigation, 28 322–329, 1949

Hilton, J G Effects of Mercurial Diuresis in Patients with Ascites Due to Cirrhosis Am J Med, 12 311–317, 1952

Himsworth H P Derangements of the Hepatic Circulation in Disease In Liver Injury Trans Sixth Conf, May 1–2, 1947 Josiah Macy Jr Foundation, 1948, pp 73–74

——— The Liver and Its Diseases Cambridge, Harvard University Press, 1950

His, W Anatomy of Human Embryos Leipzig, Vogel, 1880–1885

Hora, J Stenosis of the Splenic Vein in Childhood Virchow's Arch f path Anat 300 670–684 1937

Hoerr N L Capillary Circulation Illumination of Living Organs for Microscopic Study In Medical Physics ed by Otto Glasser Chicago, Year

Hoffma

Hjortsjo by dl,

N Y, 59 1–112 1948

——— The Topography of the Intrahepatic Duct Systems Acta anat 11 599–615 1951

Holmar

Howe

Howell D S Circulatory Manifestations of Obstruction of the Superior Vena Cava in a Patient with Portal Hypertension Rhode Island M J, 33 659–662, 1950

Huggins C and Post, J Experimental Subtotal Ligation of the Arteries Supplying the Liver Arch Surg, 35 878–886, 1937

Humph rgery S Clin

Hunt I 29 1918

——— 5, 1918

——— Certain Cholin Brit M J, 2

Hyde, d Part S The Labelled Red

Hyrtl, al Vein in Amphibians and Fishes. Sitzungsb d k Akad d Wissensch, Math-naturw Cl, 49 167–175, 1864

——— A Spiral Valve in the Portal Vein of the Gnawing Animal Sitzungsb d k Akad d Wissensch, Math naturw Cl, 1870, pp 27–32

——— Textbook of Human Anatomy, 1st Ed. Prague, Ehrlich, 1846 16th Ed. Wien, Braumuller, 1882.

Trans Eighth Conf, April 28–29, 1949. Josiah Macy, Jr. Foundation, 1950, pp 126–154
Harvey, W Exercitatio anatomica de motu cordis et sanguinis in animalibus Frankfort, Guilelmi Fitzeri, 1628 Facsimile, Paris, G Doine, 1950 English Translation by C D. Leake, Springfield, Ill, Charles C Thomas, 1928
Havens, W P, and Bluemle, L. W The Effect of Human Serum Albumin and Mercurial Diuretics on Ascites in Patients with Hepatic Cirrhosis Gastroenterology, *16* 455–464, 1950.
Hay, E B, and Webb, J K.. The Effect of Intravenous Sodium Dehydrochlorate on the Mortality Rate Following Hemorrhagic Shock. Surgery, *29*.829–831, 1950
——— and Webb, J K The Effect of Increased Arterial Blood Flow to the Liver on the Mortality Rate Following Hemorrhagic Shock. Surgery, *29* 820–828, 1951
Hay, S H, and Wood, J E, Jr. Cation Exchange Resins in the Treatment of Congestive Heart Failure Ann Int Med, *33*.1139–1148, 1950
Heidenhain, R, Editor Studies from the Physiological Institute of Breslau Leipzig, 1861–1868
——— Physiology of the Liver In Handbuch der Physiologie Ed by L.
——— ymph Formation
Heller, ...handl d. deutsch. path Gesellsch, *7* 182–189, 1904.
Henle, F G H The Contractility of the Vessels. Wchnschr. ges. Heilk, 1840, pp 329–336
——— Handbook of the Blood Vessels of Man. Braunschweig, 1868. 2nd Ed, 1882
——— Fundamentals of Human Anatomy. 2nd Ed. Braunschweig, F. Vieweg, 1883.
Henle,
Henry, York Med J., Feb 15, 1913
Hering, E The Structure of the Vertebrate Liver Sitzungsb. d k. Akad. d Wissensch Math-naturw Cl, *54* 335, 496, 1866
——— The Structure of the Mammalian Liver. Arch f mikr. Anat, *3* 88–114, 1867
——— The Liver In Handbuch der Lehre von den Geweben. Ed by S Strickler English translation, New York, William Wood, 1872, pp 407–427
Hermann, H, Jourdan, F, and Sédallian, P. On the Functional Role of the Hepatic Artery Bull Acad de med, Paris, *119*.754–757, 1938
Herrick, F C An Experimental Study into the Cause of the Increased Portal Pressure in Portal Cirrhosis J Exper Med, *9* 93–104, 1907.
Herrick, J B Pericarditic Pseudocirrhosis of the Liver. Trans. Chicago Path Soc., *5* 71–82, 1902
Herring, P T, and Simpson, S The Lymphatics of the Liver. Brit M J., 2. 1797–1798, 1906
Hickman, J, Edwards, J E, and Mann, F C · Venous Anomalies in a Dog Anat. Rec, *104*.137–146, 1949
Higgins, G M, Mann, F. C., and Priestley, J. T Experimental Pathology of

Kadmg, K A Healed Case of Intrahepatic Aneurism with Special Reference to Traumatic Aneurism of the Hepatic Artery Deutsche Ztschr f Chir, *150* 82–103, 1919
Kaiser, S Surgery of the Spleen and Portal Hypertension Rev brasil cir, *19* 591–616, 1950
Kalter, H, and Fraser, F C Production of Congenital Defects in the Offspring of Pregnant Mice Treated with Compound F Nature, *169* 665, 1952
Karabin, J E Cyst in the Ligamentum Teres of the Liver Remnant of the Umbilical Vein Am J Surg, *82* 531–532, 1951
Kark, R M, Keeton, R W, Calloway, N O, Morey, G R, Chapman, R A, and Kyle, R H A Rational Basis for the Use of Low Sodium, High Protein Diet Therapy in Laennec's Cirrhosis Arch Int Med, *88* 61–77, 1951
Kaspar, F Contribution to the Knowledge of Obstruction in the Stem of the Portal Vein and the Splenic Vein Deutsche Ztschr f Chir, *156* 1–57, 1920
Katsnel'son, Z S, Chernєak, V Z, and Rozhos, D I Histological Observations on Regenerative Processes in the Horse Liver Following Damage by Infection Doklady Akad Nauk S S S R *81* 465–468, 1951
Katz, L N, and Rodbard, S The Integration of the Vasomotor Responses in the Liver with Those in Other Systemic Vessels J Pharmacol & Exper Ther, *67* 407–421, 1939
Kaznelson, P Disappearance of Hemorrhagic Diathesis in a Case of 'Essential Thrombopenie' (Frank) after Splenectomy Wien klin Wchnschr, *29* 1451–1454, 1916
——— Indications for Splenectomy and its Mechanism of Action Wien Arch f inn Med, *7* 87–115, 1924
Kehr, H The First Case of Successful Ligation of the Hepatic Artery Because of Aneurism Munchen med Wchnschr *43* 1861–1867 1903
Keibel, F, and Mall, F P Manual of Human Embryology Philadelphia, J B Lippincott Co 1910
Kellner, A Personal communication 1952
Kellogg, H B Studies on the Fetal Circulation of Mammals Am J Physiol *91* 637–648 1930
Kelly, A O J The Nature and the Lesions of Cirrhosis of the Liver with Special Reference to the Regeneration and Rearrangement of the Liver Parenchyma Am J M Sc *130* 951–968, 1905
Kelty, R H Baggenstoss A H and Butt R The Relation of the Regenerated Liver Nodule to the Vascular Bed in Cirrhosis Gastroenterology, *15* 285–303, 1950
Kennedy R J and Rousselot, L M The Cruveilhier Baumgarten Syndrome Report of a Case Treated by Combined Splenectomy and Splenorenal Shunt Angiology, *1* 484–490 1950
Kershner, D, Hooton T C and Shearer E M Production of Experimental Hypertension in the Dog Arch Surg *53* 425–434, 1946
Kiernan F The Anatomy and Histology of the Liver Trans Roy Soc London *123* 711–770, 1833
Kliges C Anatomical Investigation on the Vascular Course of the Liver of Newborn Sheep and Full Term Calves Morph Jahrb, *68* 301–324, 1931
Klebs E Handbook of Pathological Anatomy Berlin, A Hirschwald, 1865–80

tous States. J Clin Investigation, 28 1403–1410, 1949.

on the Products of Human Plasma Fractionation. J. Clin. Investigation, 23 465–489, 1944

Jansen, A. Fatal Hemorrhage by an Unusual Erosion of the Portal Vein. Deutsch Gesundhwes, 5 435–436, 1950.

Jefferson, N C, Proffitt, M M., and Necheles, H · Collateral Arterial Circulation to the Liver of the Dog Surgery, 31·724–730, 1952.

Jeger, E A New Clamp for Establishment of Side-to-Side Anastomoses between Blood Vessels without Interruption of the Circulation. Zentrlbl f Chir, 29 604–607, 1912

——— The Operative Technique of the Eck Fistula. Beitr. z. Path. u. Ther.

———

———

sels Arch f. klin Chir, 100 893–924, 1913.

Jerusalem, E A Simplification of the Operative Technique of the Eck Fistula Zentrlbl f. Physiol, 24 837–840, 1910.

———

Johans

Johnst

Relationships of the Bile Ducts Surg, Gynec & Obst., 94 669–686, 1952

Johnston, J M Relation of Changes in the Portal Circulation to Splenomegaly in Banti's Ann Clin. Med., 4.772–782, 1931.

Jones, R A, McDonald, G O, and Last, J H.: Reversal of Diurnal Variation in Renal Function in Cases of Cirrhosis with Ascites J. Clin Investigation, 31 326–333, 1952.

Jorup, S Congenital Varices of the Esophagus Acta Paediat, 35·247–257, 1948.

Josselin de Jong, R. de On the Consequences of Thrombosis in the Region of the Portal System Mitt a d Grenzgeb d Med. u Chir, 24 160–194, 1912

——— Cirrhosis of
Rend de la
Geneva, Oct

Julian, O. C, and Dy
Surg, 63 373–378, 1951

——— and Fildes, C E Shunt Operations for Esophageal Varices S Clin. North America, 31 229–258, 1951

——— and Metcalf, W Nonobstructive Lateral Portal Vein Vena Cava Anastomosis Arch Surg, 59·433–436, 1949

Large, A, and Preshaw, D E The Eck Fistula An Experimental and Clinical Study J internat chir,
Larrabee, R C Chronic Congestive
Disease Am J M Sc, 1887
Lasch, F, and Roller, B On the Influence of
Liver Klin Wchnschr, 15 1636–1637, 1936
Laufman, H, Ross, A, Bernhard V M, Bourdeau, R V, and Furr, W S, Jr Graded Hepatic Ligations in Experimental Ascites Surgical Forum, Proc, American College of Surgeons, Sept 23–26, 1952
Lautenbach, B F On a New Function of the Liver Phila Med Times, 7 387, 1877
Lawrence, W Account of a Child Born without a Brain, which Lived Four Days Medico-Chir Trans, 5 167–224 1814
Laws, J F, and Everson, T C The Significance of Decreased Dye Clearance by the Liver Following Portacaval Anastomosis J Lab & Clin Med, 37 515–519, 1951
——— and Johnston, R The Significance of Meat Intoxication Syndrome in Eck Fistula Dogs Surgical Forum, American College of Surgeons, 1951 Philadelphia, W B Saunders Co, 1952 pp 188–189
Layne, J A, and Schemm, F R The Use of a High Fluid Intake and a Low Sodium Acid Ash Diet in the Management of Portal Cirrhosis with Ascites Gastroenterology, 9 705–717, 1947
Lazzari, J H, and Rack, F J Hepar Lobatum with Portal Hypertension Successfully Treated by Portacaval Anastomosis Arch Surg, 62 295–298 1951
Leaf, A and Mamby A R The Normal Antidiuretic Mechanism in Man and Dog Its Regulation by Extracellular Fluid Tonicity J Clin Investigation, 31 54–59, 1952
——— and Mamby, A R Antidiuretic Mechanism Not Regulated by Extracellular Fluid Tonicity J Clin Investigation, 31 60–70, 1952
Ledieu, M Aneurism and Obliteration of the Hepatic Artery J de méd de Bordeaux, 1 125–131 1856
Ledieu, P T *Contribution to the Study of Suppurative Pylephlebitis* Paris, 1879
Lee, C A Black Ramollissement of the Liver, Sudden Death Am J M Sc, 17 60–62 1835
Lee, F C On the Lymph-Vessels of the Liver Carnegie Institution, Contributions to Embryology 15 63–72, 1923
Leger L Presentation of a Case Results after 21 Months of an Anastomosis of the Portal Vein with the Vena Cava Mem Acad de chir, 76 686–687, 1950
——— Albot G, and Arvay M Portal Phlebography in Examination of Hepatosplenic Affections Presse méd, 59 1230–1232, 1951
——— Albot G, and Zerolo, F Ligation of the Hepatic Artery for Cirrhosis Mem Acad de chir, 77 710–711, 1951
chman W On the Form and Development of the Wall of the Posterior Vena Cava of the Cow and Venous Valves in the Horse and Cow Bern and Berlin, 1909
——— Clave on Sclerosis of the Portal Vein Med Klin, 22 405–408, 1926
she, S H, Johnston, B, and Ralli, E P Renal Function as a Factor in Fluid Retention in Patients with Cirrhosis of the Liver J Clin. Investigation, 30 1200–1206 1951
ott, M F, Turner, L B and Sweet, A Y. The Effect of Experimental

Klemperer, P Cavernomatous Transformation of the Portal Vein: Its Rela-

——— . Downey, New

Knight. . Dangers. Ann
Surg, 74 697–699, 1921

Knisely, M H Discussion Ninth Liver Conference.

——— r Microscopic Study,

——— tions in Living Frog
Liver Lobules Anat Rec. (Sect., Am. Ass. Anatomists), 73 69–70, 1939

———

———

Kohma
tem Deficiency Am J Physiol, 51:378–405, 1920.

Kollman, J. Development of the Spleen in Asses and Man. Verhandl schweiz Natur Ges, 83 1872.

———

Kucsko, .
tc
Hepatica. Klin. Med, osterreichische. Ztschr f wissensch u. prak Med, 5 558–564, 1950

Kuhr, P On the Diagnosis of Portal Obstruction Mitt. a. d. Grenzgeb d. Med u Chir, Jena, 37 177–189, 1923

Kunkel, H G, Labby, D H, Ahrens, E H, Jr, Shank, R E, and Hoagland, C. L · The Use of Concentrated Human Serum Albumin in the Treatment of Cirrhosis of the Liver. J Clin. Investigation, 27·305–318, 1948

gation, 26 343–351, 1947

Laennec, R T H Letter to Dupuytren on the Tunics which Envelop Certain Viscera and Furnish Membranous Sheaths to their Vessels. J de Méd. Ed by Corvisart, Leroux & Boyer, 5·539–574, 1802? (11th Vendémaire)

———
cc

Lampe,
m

Lamson, P D, and Roca, J The Liver as a Blood Concentrating Organ. J Pharmacol & Exper Therap, 17·481–496, 1921.

Large, A, Johnston, C G, and Preshaw, D E The Portacaval Venous Shunt With Special Reference to Side-to Side Portacaval Anastomosis Ann Surg, 135·22–33, 1952

Large, A , and Preshaw, D E.: The Eck Fistula An Experimental and Clin

Lautenbach, B F On a New Function of the Liver Phila Med Times, 7 387, 1877.
Lawrence, W Account of a Child Born without a Brain, which Lived Four Days Medico Chir Trans , 5 167–224, 1814
Laws, J F , and Everson, T. C The Significance of Decreased Dye Clearance by the Liver Following Portacaval Anastomosis J Lab & Clin Med , 37.515–519, 1951
——— and Johnston, R Tl
in Eck Fistula Dogs
1951 Philadelphia, V
Layne, J A , and Schemm, F
Sodium Acid-Ash Diet in the Management of Portal Cirrhosis with Ascites Gastroenterology, 9 705–717, 1947
Lazzari, J H , and Rack, F J Hepar Lobatum with Portal Hypertension Successfully Treated by Portacaval Anastomosis Arch Surg , 62 295–298 1951
Leaf, A and Mamby, A R The Normal Antidiuretic Mechanism in Man J Clin In-

gulated by Ex
)–70 1952
J de med de

Bordeaux, I 125–131, 1856
Ledieu, P T Contribution to the Study of Suppurative Pylephlebitis Paris, 1879
Lee, C A Black Remollissement of the Liver, Sudden Death Am J M Sc

Lee, F

Leger, I

687 1950

Leslie, S H , Johnston, B , and Ralli, E P Renal Function as a Factor in Fluid Retention in Patients with Cirrhosis of the Liver J Clin Investigation, 30 1200–1206, 1951
Turner, L B , and Sweet, A Y The Effect of Experimental

Venous Obstruction on Salt and Water Distribution and Excretion in Man J Clin Investigation, 31 885–893, 1952
Levy, L. K, and Burch, G F Studies on Venous Pressure in Hepatic Cirrhosis Ann. Int Med., 29 274–277, 1948.
Lewis, J M, Buie, R M, Sevier, S. M., and Harrison, T. R. The Effect of Posture and of Congestion of the Head on Sodium Excretion in Normal Subjects Circulation, 2 822–826, 1950.
Lichtman, S S Diseases of the Liver, Gallbladder and Bile Ducts Philadelphia, Lea & Febiger, 1949.
——— and Sohval, A R Clinical Disorders with Associated Hepatic and Renal Manifestations with Especial Reference to the So-Called "Hepatorenal Syndrome" Am. J Digest Dis, 4 26–31, 1937.
. Mem
ension.
al Sys-
4 433-
443, 1951
——— and
from
at the
Lloyd, C W
Pituit.
tion, 30 657, 1951
——— and Williams, R H. Endocrine Changes Associated with Laennec's Cirrhosis of the Liver Am J Med, 4 315–327, 1948
Loeb, J Two Notable Cases of Thrombosis of the Portal Vein. Bonn, J Trapp, 1909
Loeb, R F, Atchley, D W, and Palmer, W. W On the Equilibrium Condition between Blood Serum and Serous Cavity Fluids. J. Gen. Physiol, 4 591–595, 1922
———, Reeves, E B, and Glaser, H P. Responses to the Injection of Epinephrine in Hepatic Disease. J Clin Investigation, 10.19–30, 1931
Loeffler, L The Structure of the Lobule of the Liver. Ztschr f Anat. u Entwcklngsgesch, 84 511–522, 1927.
——— Further Investigation on the Effects of Ligation of the Hepatic Artery Arch f klin Chir, 149 37–384, 1928
er Liga
sults of
Surg,
n Cal
ifornia Med, 73 209–213, 1950.
Lord, J E, Jr A Modification of the Crosby-Cooney Operation for Intractable Ascites Due to Cirrhosis of the Liver. J.A.M.A, 136.767–769,
Lowe, Rigid Dietary Sodium
Cirrhosis of the Liver.

Lucké, B The Pathology of Fatal Epidemic Hepatitis Am J Path, 20 471–593, 1944.
——— *The Structure of the Liver after Recovery from Epidemic Hepatitis* Am J Path, 20 595–619, 1944
——— and Mallory, T The Fulminant Form of Epidemic Hepatitis Am J *Path*, *22* 867–918, 1946
Ludwig, H The Function of the "Blood Depot" Ztschr f exper Med, 80 36–52, 1932
Lyons, R H, *Harris J F*, and Lloyd, C W Study of Sodium and Water Metabolism in Patients with and without Liver Disease during Continued Administration of Pitressin Tannate Am J Med, 11 518 1951
McCarrell, J D, and Drinker, C K Cervical Lymph Production During Histamine Shock in the Dog Am J Physiol, 133 64–69, 1941
McDermott, W V A One Stage Pancreaticoduodenectomy with Resection of the Portal Vein for Carcinoma of the Pancreas Ann Surg, 136 1012–1017, 1952
McEwen, H D, and Kropp, B N Sinusoidal Dilatation in Liver and Adrenal Cortex of Tumor Bearing Rats Proc Soc Exper Biol & Med, 76 97–99, 1951
MacGillavry, T H The Anatomy of the Liver Sitzungsb d Akad d Wissensch Math-naturw Cl, 50 207–224, 1865
Macgregor, C A Study of Liver Function in the Dog with Complete Biliary Obstruction Surgical Forum, American College of Surgeons 1952 Philadelphia, W B Saunders Co 1953
McIndoe A H Vascular Lesions of Portal Cirrhosis Arch Path, 5 23–40, 1928
McKee, F W, Schloerb, P R, *Schilling J A Tishkoff G H* and Whipple, G H Protein Metabolism and Exchange as Influenced by Constriction of the Vena Cava J Exper Med, 87 457–470, 1948
———, *Yuile, C L, Lamson, B G, and Whipple G H* Albumin and Globulin Circulation in Experimental Ascites J Exper Med, 95 161–172, 1952
MacKenzie, D W, Jr Whipple A O and Wintersteiner, M P Direct Observations on the Circulation of Blood in Transilluminated Mammalian Spleens Proc Soc Exper Biol & Med, 44 139–142, 1940
McLeod, J J R and Pearce R G The Outflow of Blood from the Liver as Affected by Variations in the Condition of the Portal Vein and Hepatic Artery Am J Physiol 35 87–105 1914
MacMahon H E Congenital Anomalies of the Liver Am J Path, 5 499–507 1929
——— Infective Cirrhosis Am J Path 7 77–86, 1931
———, Lawrence, J S, and Maddock S J Experimental Obstructive Cirrhosis Am J Path 5 631–642 1929
——— and Mallory, F B Obstructive Cirrhosis Am J Path, 5 645–657, 1929
———, Murphy, A S and Bates, M I Endothelial Cell Sarcoma of Liver Following Thorotrast Injections Am J Path, 23 585–611, 1947
McMichael, J The Pathology of Hepatolienal Fibrosis. J Path & Bact, 39 481–501, 1934
——— The Portal Circulation II The Action of Acetylcholine J Physiol, 77 399–420, 1933

Venous Obstruction on Salt and Water Distribution and Excretion in Man J Clin Investigation, 31 585–593, 1952.

Levy I K and Burch, G E Studies on Venous Pressure in Hepatic Cirrhosis Ann Int Med, 29 274–277, 1948.

Lewis, J M, Buie, R M, Sevier, S M, and Harrison, T. R · The Effect of Posture and of Congestion of the Head on Sodium Excretion in Normal Subjects Circulation, 2 822–826, 1950.

Lichtman, S S Diseases of the Liver, Gallbladder and Bile Ducts Philadel

——— and

...ep-atorenal Syndrome" Am J Digest Dis, 4:26–31, 1937.

Lieberkuhn On Methods of Investigating the Structure of the Viscera Mem Akad d Wissenschaften, 1748

Linton R R Portacaval Shunts in the Treatment of Portal Hypertension New England J Med, 238 723–727, 1848

——— Sys-

t

——— 433–443, 1951

——— and Warren, R The Emergency Treatment of Massive Bleeding from Esophageal Varices by Transesophageal Suture of These Vessels at the

Lloyd, C W,

Pituitar

tion, 30 657, 1951

——— and Williams, R H Endocrine Changes Associated with Laennec's Cirrhosis of the Liver Am J Med, 4 315–327, 1948

Loeb, J Two Notable Cases of Thrombosis of the Portal Vein, Bonn, J Trapp, 1909

Loeb, R F Atchley, D W, and Palmer, W W. On the Equilibrium Condition between Blood Serum and Serous Cavity Fluids, J Gen. Physiol, 4 591–595, 1922

——— Reeves E B, and Glasier, H P Responses to the Injection of Epinephrine in Hepatic Disease J Clin Investigation, 10 19–30, 1931

Loeffler L The Structure of the Lobule of the Liver Ztschr f. Anat u. Entwklngsgesch, 84 511–522, 1927

——— Further Investigation on the Effects of Ligation of the Hepatic

———

Loggan,

Pancreaticoduodenal Resections Reported in the Literature Surg, Gynec & Obst, Internat Abst Surg, 93 521–541, 1951

Longmire, W P, Jr The Surgical Treatment of Portal Hypertension California Med, 73 209–213, 1950.

Lord, J E, Jr A Modification of the Crosby-Cooney Operation for Intractable Ascites Due to Cirrhosis of the Liver J A M A, 136 767–769, 1948

Lowe, C R, and Overy, D C An Evaluation of Rigid Dietary Sodium Restriction in the Management of Ascites in Cirrhosis of the Liver Ann Int Med, 34 1396–1402, 1951

J Clin Investigation,

Removal of the Liver

——— Functional Significance In York, Paul B Hoeber, 1932,

——— The Portal Circulation and Restoration of the Liver after Partial Removal Surgery, 8 225–238, 1940
——— The Liver and Medical Progress J A M A, 117 1577–1582, 1941
——— The Circulation of the Liver Quart Bull Indiana Univ M Center, 4 43–53, 1942.
——— and Bollman, J L Disturbance of Metabolism in Cirrhosis of the Liver Compt Rend de la Premiere Conf Internat de path. géogr Geneva, Oct 8–10, 1931 Geneva, Kundig, pp 190–216
———, Fishback, F C, Gay, J G, and Green, G F Experimental Pathology of the Liver Studies III, IV, and V Arch Path, 12 787–793, 1931
Mann, J D, Mann, F C,
Loss of Intestinal L
Mann, M, and West, G B
J Pharmacol 5 173–177 1950

97, 1951
Marau A
Bibl
Markowitz,
Co, 1949
——— The Function of the Hepatic Artery In Liver Injury Trans Eighth Conf, April 28–29, 1949 Josiah Macy, Jr Foundation, 1950
——— The Hepatic Artery Editorial Surg, Gynec & Obst, 95 644–646, 1952
———, Lotto, W, Archibald, J, and Downie, H G Technique and Effects of Portacaval Anastomosis (Eck Fistula) Surg, Gynec & Obst 95 407–409 1952
——— and Rappaport, A M The Hepatic Artery Physiol Rev, 31 188–204 1951
——— Rappaport A, and Scott, A C The Function of the Hepatic Artery in the Dog Am J Digest Dis, 16 344–347, 1949
———, Rappaport, A and Scott, A C Prevention of Liver Necrosis Following Ligation of Hepatic Artery Proc Soc Exper Biol & Med, 70 305, 1949
Martin P Division and Suture of the Portal Vein Brit, M. J, 2 586, 1951
Martz B L Kohlstaedt, K G, and Helmer, O M Use of a Combination of Anion and Cation Exchange Resins in the Treatment of Edema and Ascites Circulation, 5 524–532, 1952
Mautner H and Pick, E. P. Circulatory Disturbance Produced by Shock Munchen med Wchnschr, 62 1141–1143, 1915
Mayer L Wounds of the Liver and Gall Bladder, Munchen, R Oldenburg 1872

McMich of Adrenalin and
P 1932.

——— Physiol, *27*.73–86, 1938.

McNamara, W L, Baker, L A., and Costich, K.: Aneurism of the Hepatic Artery Ann Surg, *123*·427–434, 1946.

Mackay, R. P The Familial Occurrence of Multiple Sclerosis and its Implications A Research Nerv & Ment Dis, Proc, *28* 150–177, 1950.

Madden, J L Personal Communication

——— Ligation of Hepatic and Splenic Arteries in Treatment of Cirrhosis of the Liver Surgical Forum, Proc, American College of Surgeons, Sept. 23–26, 1952

——— and Loré, J M Surgical Anatomy of the Portal System Surgical Forum, American College of Surgeons, 1951. Philadelphia, W. B Saunders Co, 1952, pp 133–139

———, Loré, J M, and Gerold, F P Pathogenesis of Ascites in Cirrhosis of the Liver Surgical Forum, Proc, American College of Surgeons, Sept 23–26, 1952

Maegraith, B G Micro-Anatomy of the Hepatic Vascular System. In. Liver Injury Trans Tenth Conf, May 21–22, 1951. Josiah Macy, Jr Foundation, 1951

———, Andrews, W H H, and Wenyon, C. E M.· Active Constriction of Hepatic Venous Tree in Anaphylactic Shock. Relation of Centrilobular Lesions Lancet, 2 56–57, 1949

———, Andrews, W H H, and Wenyon, C. E M. Studies on the Liver Circulation Ann Trop Med & Parasitol., *43*·225–227, 1949.

Magendie, F Précis élémentaire de physiologie. Paris, Méguignon Marvis, 1816–17

Mahon

Mall, F
Dog Abhandl der Akad d Wissensch, Leipzig, Math-Phys Cl, 14 153, 1888

———
A

———
Hosp *12* 146–148, 1901

——— A Study of the Structural Unit of the Liver. Am. J. Anat., *5* 227–308, 1906

Mallet-Guy, P, Bèzes, H., and Sermenard, J: Sympathectomy of the Hepatic Artery for Hepatitis with Icterus Dating from Six Months. Lyon chir, *45* 242–244, 1950

——— R A, Experi- Anastomosis chir, *47* 155–179, 1952.

Mallory, F B Cirrhosis of the Liver Five Different Types of Lesions from Which It May Arise Bull Johns Hopkins Hosp, *22* 67–75, 1911

Malpighi, M De hepate In De viscerum structura exercitatio anatomica London, J Martyn, 1669, pp 1–74.

——— Exercitatio de hepate In Clericus, Daniel and Mangetus Bibliotheca anatomica. Genevae, 1685, Vol 1, pp 333–344.

Mankin, H, and Lowell, A Osmotic Factors Influencing the Formation of

Ascites in Patients with Cirrhosis of the Liver J Clin Investigation 27 145-152, 1948

Mann, F C The Effects of Complete and Partial Removal of the Liver Medicine, 6 419-499, 1927

——— The Cytology of the Liver and Its Functional Significance In

———

———

——— The Circulation of the Liver Quart Bull Indiana Univ M Center, 4 43-53, 1942

——— and Bollman, J L Disturbance of Metabolism in Cirrhosis of the Liver Compt Rend de la Premiere Conf Internat de path géogr Geneva, Oct 8-10, 1931 Geneva Kundig, pp 190-216

———, Fishback, F C, Gay, J G, and Green, G F Experimental Pathology of the Liver Studies III, IV, and V Arch Path, 12 787-793, 1931

Mann, J D, Mann, F C, and Bollman J L Hypoprothombinemia Due to Loss of Intestinal Lymph Am J Physiol, 158 311-314, 1949

Mann, M, and West, G B Nature of Hepatic and Splenic Sympathin Brit

97, 1951

Marıau, A A Case of Anastomosis between the Splenic and Left Renal Veins Bibliog anat, Paris, 8 309-311, 1900

Markowitz, J Experimental Surgery 2nd Ed Baltimore, Williams & Wilkins Co, 1949

——— The Function of the Hepatic Artery In Liver Injury Trans Eighth Conf, April 28-29, 1949 Josiah Macy, Jr Foundation, 1950

——— The Hepatic Artery Editorial Surg, Gynec & Obst, 95 644-646 1952

———, Lotto, W, Archibald, J, and Downie, H G Technique and Effects of Portacaval Anastomosis (Eck Fistula) Surg, Gynec & Obst, 95 407-409, 1952

———, and Rappaport, A M The Hepatic Artery Physiol Rev, 31 188-204, 1951

———, Rappaport, A, and Scott, A C The Function of the Hepatic Artery in the Dog Am J Digest Dis, 16 344-347, 1949

———, Rappaport, A, and Scott, A C Prevention of Liver Necrosis Following Ligation of Hepatic Artery Proc Soc Exper Biol & Med, 70 305, 1949

Martin, P Division and Suture of the Portal Vein Brit M J, 2 586, 1951

Martz, B L, Kohlstaedt, K G, and Helmer, O M Use of a Combination Edema

Shock

lenburg

1872

Maximow, A. A., and Bloom, W. Textbook of Histology. 6th Ed., Philadelphia, W. B. Saunders Co., 1952

Mayo, W. J. The Surgical Treatment of Hepatic Cirrhosis. Ann. Surg., 80. 419–424, 1924

Meyer, F. G. Cavernous Changes of the Portal Vein. Med. Klin., 16 880–883, 1920

Meyer, H. ... ein Compression Healed by the ... 50.576–581, 1906.

Meyer, O. ... r. Virchow's Arch. f. path Anat., 225 213–234, 1918

Michels, N. A. The Hepatic, ... Relation to the Biliary ...

Miller, F. M., and Clagett, O. ... aticoduodenectomy for ... Surg., 134 1013–1017, 1951.

———, Dockerty, M. B., Wollaeger, E. E., and Waugh, J. M. Carcinoma in the Region of the Papilla of Vater. A Study of Cases in Which Resection Was Performed. Surg., Gynec. & Obst., 92·172–181, 1951.

Milne, L. S. The Histology of Liver Tissue Regeneration. J. Path. & Bact., 13 127–158, 1909

Milnes, R. F. Hepatic Artery Ligation in Rabbits Followed by Thoracic Caval Constriction. Proc. Soc. Exper. Biol. & Med., 77.653–655, 1951.

——— An Evaluation of Hepatic and Splenic Artery Ligation in Dogs with Experimental Ascites. Surgery, 32 704–711, 1952.

——— and Child, C. G., III. Acute Occlusion by Ligature of the Portal Vein in the *Macacus Rhesus* Monkey. Proc. Soc. Exper. Biol. & Med., 70 332–334, 1949

Mino, R. A., Murphy, A. I., and Livingstone, R. G. Sarcoidosis Producing Portal Hypertension. Treatment by Splenectomy and Splenorenal Shunt

Minot, C. S. ... out C... Hist., 29 185–216, 1901

Moersch, H. J. Treatment of Esophageal Varices by Injection of Sclerosing Solution. J.A.M.A., 135 754–757, 1947

Mondine, C., and Rattone, G. Studies on the Circulation of the Liver. Arch. ital. de biol., Turin, 12 156–177, 1889

Monprofit, A. Surgical Treatment of Cirrhosis of the Liver. Presse méd., 2. 667–670, 1904

——— The Talma Operation. Méd. mod., 15 329–332, 1904

Moon, V. H. Experimental Cirrhosis in Relation to Human Cirrhosis. Arch. Path., 18 381–421, 1934

——— Circulatory Failure of Capillary Origin. J.A.M.A., 114·1312–1318, 1940

Moore, F. D., and Ball, M. R. The Metabolic Response to Surgery. Springfield, Ill., Charles C Thomas, 1952

Moore, G. E., and Bridenbaugh, R. B. Roentgen Demonstration of the Venous Circulation in the Liver. Radiology, 57 685–689, 1951

Morgagni, G. B. Epistolae anatomica, duae novas observations. Venice, Gremondiniana, 1862

——— Recherches anatomiques sur le siège et les causes des maladies. Paris Caille & Ravier, 1824

Morison, R A Case of Ascites Due to Liver Cirrhosis Treated by Operation Ann Surg, 38 361–366, 1903

——— Operative Cure of Ascites due to Liver Cirrhosis (Talma Morison Operation) Proc Roy Soc Med, Surg Sect, 5 37–43, 1912

Morris, A N, and Miller, H H Chronic Portal Vein Occlusion and Portal *Hypertension in the Dog Surgery*, *30* 768–774, *1950*

Moschcowitz, E Laennec Cirrhosis Its Histogenesis, with Special Reference to the Role of Angiogenesis Arch Path, 45 187–215, 1948

——— The Pathogenesis of Splenomegaly in Hypertension of the Portal Circulation "Congestive Splenomegaly" Medicine, 27 187–219, 1948

——— The Morphology and Pathogenesis of Cardiac Fibrosis of the Liver Ann Int Med, 36 933–955, 1952

Muller De glandularum secernentium structurá penitori earumque primá formatione in homine atque in animalibus Leipzig 1830

Muller, W The Problem of Operative Treatment of Ascites in Compression of the Portal Vein Arch f klin Chir 66 210–211, 1902

Muersing, F The Anastomosis of the Vena Porta and the Vena Cava Nederl tijdschr v geneesk, *56* 1678–1684, 1912

Mulligan, L V Venous Shunts in Portal Hypertension S Clin North America, 30 1465–1478, 1950

Myers, J D The Hepatic Blood Flow in Laennec's Cirrhosis with an Estimate of the Relative Contributions from Portal Vein and Hepatic Artery J Clin Investigation, 29 836 1950

Nabatoff, R A The Portal Systemic Venous Shunt in the Treatment of Portal Hypertension J Mt Sinai Hosp 18 292–295 1952

——— The Surgical Treatment of Portal Hypertension Am J Digest Dis, 19 251–254, 1952

Naegeli, T The Rate of Circulatory Flow in the Portal System Deutsch Ztschr f Chir, 222 92–96, 1930

——— Late Findings after Formation of an Eck Fistula in the Dog Helvet med acta, 6 897–899 1940

——— and Lauche A Findings in the Liver and Spleen of a Dog Injected for Two years with Thorium Dioxydsol Klin Wchnschr 11 2029–2030 1932

——— and Meyerthaler F Experimental Investigation of Arteriovenous Anastomoses of the Vessels of the Liver Deutsch Ztschr f Chir, 240 88–91 1933

Narath A The Arterio Venous Anastomosis of the Portal Vein as Means of Treating Necrosis of the Liver after Ligation of the Hepatic Artery Zentralbl f Chir 1 1–4 1915

——— The Origin of Anemic Necrosis of the Liver after Ligation of the Hepatic Artery and its Cure by Arterio Portal Anastomosis Deutsche Ztschr f Chir 135 305–376, 1916

Nanta A Experimental Studies on the Relationship of the Liver to Blood Infection Ztsch f d ges exper Med, 80 303–330, 1932

Neal H V and Rand H W Comparative Anatomy Philadelphia The Blakiston Co 1936

Nelson W P and Welt, L G The Effects of Pitressin on the Metabolism and Excretion of Water and Electrolytes on Normal Subjects and Patients with Cirrhosis and Ascites J Clin Investigation 31 592, 1952

Neuhof, H Experimental Ligation of the Portal Vein: Its Application to the Treatment of Suppurative Pylephlebitis Surg, Gynec. & Obst.,

1952

———, Mann, F C, Bollman, J L, Grindlay, J. H, and Flock, E V: Alterations of Protein Constituents of Lymph by Specific Injury to the Liver Am J Physiol., 164:119–122, 1951.

North, J. P, and Wollerman, O. J., Venous Mesenteric Occlusion in the Course of Migrating Thrombophlebitis Surg., Gynec. & Obst, 95 665–670, 1952

Olds, J M, and Stafford, E. S On the Manner of Anastomosis of the Hepatic and Portal Circulations. Bull Johns Hopkins Hosp., 47:176–184, 1930

Oliver, G: The Action of Animal Extracts on the Peripheral Vessels J. Physiol, 21 XXII–XXIII, 1897.

——— and Schafer, E A On the Physiological Action of Extract of the Suprarenal Capsules J Physiol, 16 i–iv, 1894.

Oppel, A A Method of Showing the Fine Structural Relations of the Liver Anat Anz, 5:143–145, 1890

——— The Reticular Fibers of the Human Liver and Spleen. Anat. Anz,

Oré.

Rov des Sciences, 43:463–467, 1856.

——— Functions and Obliterations of the Portal Vein, Bordeaux, 1861. Reviewed J d'anat et physiol norm et path., 1:550–564, 1864.

Orr, T G Some Observations on the Treatment of Carcinoma of the Pancreas Surgery, 32 933–947, 1952.

O'Shaughnessy, L, and Slome, D Etiology of Traumatic Shock Brit J. Surg, 22 589–618, 1935.

Osler, W Cases of Obliteration of the Portal Vein (Pylephlebitis Obliterans). J. Anat & Physiol, 16 208–216, 1881–82

——— Cirrhosis of the Liver Fatal Hemorrhage from Esophageal Varix

———

Paget, J St. Barth

Pal, J , 1888

Palmed Berlin, J Sittenfeld, 1914

Palmer, E D: Determination of Venous Pressure within Esophageal Varices. J.A.M.A.,

Papper, S, and R ater and Sodium

Med, 40 523–530, 1952

———

Parsons,

1951.

Patek, A J, Jr, Mankin, H., Colcher, H, Lowell, A, and Earle, D P, Jr The Effects of Intravenous Injection of Concentrated Human Serum Albumin upon Blood Plasma, Ascites and Renal Functions in Three Patients with Cirrhosis of the Liver J Clin Investigation 27 135–144, 1948

——— and Post, J Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex J Clin Investigation, 20 481–505, 1941

———, Post, J, Ratnoff, O D, Mankin, H, and Hillman, R W Dietary Treatment of Cirrhosis of the Liver J A M A, 138 543–549, 1948

Patten, B M Human Embryology Philadelphia, The Blakiston Co, 1948

Pattison, A C. Use of Portacaval Shunts in Portal Hypertension Arch Surg, 58 590–600, 1949

Patton, T B, and Johnston, C G Method for Control of Bleeding from Esophageal Varices Arch Surg, 50 502–506, 1949

Pavlov, I P. On a Modification of the Eck Fistula between the Portal Vein and the Inferior Vena Cava Arch biol nauk, St Petersburg, 2 580–585, 1893

Payne, J F Discussion of the Morbid Anatomy and Pathology of Chronic Alcoholism Tr. Path Soc London, 40 310–354, 1899

Pean, J E Lessons of the Surgical Clinic at the Hospital Saint Louis During the Years 1874–1876 Paris, Germer Bailliere, 1876

Peck, M. E, and Grover, R F Cardiovascular Responses to Acute Ligation of Portal Vein Arch Surg, 64 665–680, 1952

Pecquet, J Experimenta nova academica Paris, Ex officina Cramosiana, 1654

Pel, P K Diseases of the Liver, Biliary Tract and Portal Vein Jena, Fischer, 1909

Pemberton, J de J, and Kiernan, P Surgery of the Spleen S Clin North America, 25 880–889, 1945

Perera, G. A The Plasma Volume in Laennec's Cirrhosis of the Liver Ann Int Med, 24 643–647, 1946

Person, E C Personal Communication

Peters, J C Report on Phlebitis of the Splenic Vein and Vena Porta Tr N Y Path Soc 2 268–279, 1877

Pfuhl, W The Form and Vascular Relations of the Liver Lobe in Man Ztschr f Anat u Entwicklungsgesch, 66 361–384, 1922

——— Lobule Size and Capillary Length in the Human Liver Ztschr f Zellforsch u mikrosk Anat, 4 216–225, 1926

——— Experimental Investigations Concerning the Kupffer Stellate Cells of the Liver Ztsch f Anat u Entwicklungsgesch, 81 90–113, 1926

——— The Liver In Handbuch mikroskopischen Anatomie des Menschen Ed by Mollendorff Berlin, Springer, 1932, Vol 5, pt 2 pp 235–460

Phemister, D B, and Humphreys, E M Gastroesophageal Resection and Total Gastrectomy in the Treatment of Bleeding Varicose Veins in Banti's Syndrome Ann Surg, 16 397–406, 1947

Pichancourt, M Contribution to the Study of the Syndrome of Portal Hypertension The Tension of the Fluids of Ascites Thesis Paris, G Steinheil, 1913

Pick, F Chronic Pericarditis Occurring with Liver Cirrhosis Ztschr f klin Med, 29 385–409, 1896

Pick, L Total Obliteration of the Portal Vein by Hemangioma and the Development of Hepatoduenal Collaterals Virchows Arch f path Anat, 197 490–530, 1909

Piersol G A Human Anatomy 9th Ed. Philadelphia, J B Lippincott Co, 1930.

[illegible] r The Ef- [illegible] Solution. [illegible] ation, 29. [illegible] enum Ex [illegible], 1582.

[illegible] Occlusion, Case of Multiple Venous Thromboses. Am J. Med, 8.401–408, 1950

Pohlman, A G The Course of the Blood through the Heart of the Fetal Mammal with a Note on the Reptilian and Amphibian Circulations Anat Rec, 3 75–108, 1909.

——— The Comparative Physiology of the Circulatory Changes at Birth. Ztschr f Morph u. Anthr., 24.191–203, 1924.

Ponfick, E Experimental Contribution on the Pathology of the Liver. Virchows Arch f path Anat, Suppl., 138 81–117, 1894.

Popper, H The Sphincter Mechanisms of the Liver Veins. Berl klin. Wchnschr, 10 2129–2131, 1931

——— Histologic Distribution of Vitamin A in Human Organs under Normal and under Pathological Conditions. Arch. Path, 31·766–802, 1941

——— Correlation of Hepatic Ligation and Structure Based on Liver Biopsy Studies In Liver Injury Trans. Ninth Conf, April 27–28, 1950 Josiah Macy, Jr Foundation, 1950.

———, Elias, H, and Petty, D E Vascular Pattern of the Cirrhotic Liver. Am J Clin Path, 22 717–728, 1952.

Portis, S A, and Weinberg, S Recent Advances in the Medical Treatment of Cirrhosis of the Liver. J A M A, 149.1265–1272, 1952

Post, J, and Patek, A J Serum Proteins in Cirrhosis of the Liver. I. Relation to Prognosis and to Formation of Ascites. Arch Int. Med, 69.67–82, 1942.

——— and Patek, A J, Jr Serum Proteins in Cirrhosis of the Liver. II Nitrogen Balance Studies on Five Patients. Arch Int Med, 69 83–89, 1942

———, Rose, J. V, and Shore, S M Intravenous Use of Salt-Poor Human Albumin. Effects in Thirty-Four Patients with Decompensated Cirrhosis Arch Int Med, 87 775–788, 1951

Postlethwait, R W, and Moseley, V. Esophageal Varices Treatment of Portal Hypertension by Portacaval Shunt. J South Carolina M. A, 46 305–308, 1950

Potts, W J, Smith, S, and Gibson, S Anastomosis of the Aorta to a Pulmonary Artery J A M A., 132.627–631, 1946.

Power, W Contributions to Pathology Maryland Med & Surg J, 1·306–318, 1840.

Preble, R. B Conclusions Based on Sixty Cases of Fatal Gastrointestinal Hemorrhage Due to Cirrhosis of the Liver Am. J. M. Sc, 119 263–279, 1900

Prentice, T C, Siri, W, and Joiner, E E: Quantitative Studies of Ascitic Fluid Circulation with Tritium-Labelled Water. Am. J Med, 13 668–673, 1952.

Prinzmetal, M, Ornitz, E. M, Jr, Simkin, B, and Bergman, H. C.. Arterio-

Venous Anastomoses in Liver, Spleen, and Lungs Am J Physiol, 152 48–51, 1948

Purcell, H K, Shen, J. T Y, and Staples, D E Operative Relief for Portal Hypertension in a Three Year Old Child J. Missouri M A, 47 917–918, 1950

Purcell, H K, Connor, J J, Alexander, W F, and Scully, N M Observations on the Major Radicles of the Extrahepatic Portal Systems Arch Surg, 62 670–677, 1951

Quercolo, G B On the Function of the Liver as Protection against Intoxication from the Intestine Untersuch z Naturlehre d Menschen u. d Thiere, 15 228–240, 1895

Quiring, D P Functional Anatomy of the Vertebrates New York, McGraw-Hill Book Co, 1950

Rack, F J, Mincks, J R, and Simeone, F A Observations on Etiology of Esophageal Varices Arch Surg, 65 422–429, 1952

Raikem A F J Observations, Reflections and Notes on Some Morbid Affections of the Portal Vein, and Especially on Inflammation, Obliteration and Ossification of the Vascular Trunk Mém Acad roy med Belgique, 1 38–82, 1848 Trans Edinburgh Med & Surg J 73 350–388, 1850

Ralli, E P, Leslie, S H, Stueck, G H, Jr, and Laken, B Studies of the Serum and Urine Constituents in Patients with Cirrhosis of the Liver During Water Tolerance Tests Am J Med, 11 157–168, 1951

Ranvier L The Liver J de Micrographie, Paris 9 7–14 55–63, 103–109, 155–163, 194–201 240–247, 287–295 334–343, 389–396 438–445, 1885 10 5–10, 55–58, 160–166 211–214, 355–362, 443–447, 1886

——— Traité technique d histologie 2nd Ed Paris, Savy, 1889

Rappaport, A M Experimental Ischemia of the Liver and Hepatic Artery In Liver Injury Tenth Conf, May 21–22, 1951 Josiah Macy, Jr Foundation, 1951, pp 146–179

———, Borowy Z J, and Lotto W N Experimental Hepatic Coma Surgical Forum, American College of Surgeons, 1952 Philadelphia, W B Saunders Co 1953

Rapport D Canzanelli A, and Guild R Effects of Ablation of the Pituitary, Adrenal and Thyroid on Liver Regeneration Nucleic Acid Partition etc Federation Proc, 7 98, 1948

Ratnoff, O D, and Patek, A J, Jr Natural History of Laennec's Cirrhosis of the Liver Medicine 21 207–262, 1942

Ravdin I S and Vars, H M Further Studies on Factors Influencing Liver Injury and Liver Repair Ann Surg 132 362–369, 1950

———, Vars H M Goldschmidt, S, and Klingensmith L E Anesthetic and Liver Damage J Pharmac & Exper Ther, 64 111–125, 1938

——— and Vars H M Studies in Factors Influencing Liver Injury and Repair Rev Gastroenterol 18 637–641, 1951

Ravenna P Banti Syndrome Arch Int Med 66 879–892, 1940

Reddingius R A Experimental Occlusion of the Portal Vein and Hepatic Collateral Circulation Verhandl d deutsch path Gesellsch, 15 191–193 1912

Reich N F Portal System Thrombosis Occurring in Portal Hypertension Ann Int Med, 17 270–272, 1942

——— Primary Portal Phlebosclerosis Arch Int. Med., 69 117–127, 1942

Reinhoff W F, Jr Ligation of the Hepatic and Splenic Arteries in the Treat-

Piersol, G A Human Anatomy. 9th Ed Philadelphia, J B Lippincott Co, 1930

Pilcher J. D., and Sollmann, T Studies on the Vasomotor Center The Effects of Hemorrhage and Reinjection of Blood and Saline Solution Am J Physiol, 35 59–69, 1914.

Pitts, R F, and Duggan, J J Studies in Diuretics J. Clin. Investigation, 29: 372–379, 1950

Plinius Secundus, G Historia mundi naturalis. Francoforti ad Moenum. Ex officina Martini Lechleri impensis. Sigismundi Geyerabendi, 1582.

Plough, I. C, and Bevans, M Chiari's Syndrome Hepatic Vein Occlusion, Case of Multiple Venous Thromboses. Am. J. Med., 8.401–408, 1950

Pohlman, A G The Course of the Blood through the Heart of the Fetal Mammal with a Note on the Reptilian and Amphibian Circulations Anat. Rec, 3 75–108, 1909

——— Circulatory Changes at Birth. , 1924.

Ponfick Pathology of the Liver Virchows Arch f path Anat., Suppl, 138 81–117, 1894

Popper, H The Sphincter Mechanisms of the Liver Veins. Berl. klin. Wchnschr, 10 2129–2131, 1931.

——— Histologic Distribution of Vitamin A in Human Organs under Normal and under Pathological Conditions. Arch. Path, 31·766–802, 1941

——— Correlation of Hepatic Ligation and Structure Based on Liver Biopsy Studies In Liver Injury Trans. Ninth Conf, April 27–28, 1950. Josiah Macy, Jr Foundation, 1950.

———, Elias, H, and Petty, D E Vascular Pattern of the Cirrhotic Liver. Am J. Clin Path, 22 717–728, 1952.

Portis, S A, and Weinberg, S. Recent Advances in the Medical Treatment of Cirrhosis of the Liver J A M A, 149 1265–1272, 1952

Post, J. and Patek, A. J. Serum Proteins in Cirrhosis of the Liver I. Relation to Prognosis and to Formation of Ascites Arch. Int. Med, 69 67–82, 1942

——— and Patek, A J, Jr Serum Proteins in Cirrhosis of the Liver. II. Nitrogen Balance Studies on Five Patients. Arch Int. Med, 69.83–89, 1942

———, Rose, J V., and Shore, S M Intravenous Use of Salt-Poor Human Albumin Effects in Thirty-Four Patients with Decompensated Cirrhosis. Arch Int Med, 87·775–788, 1951.

Postlethwait, R W, and Moseley, V Esophageal Varices Treatment of Portal Hypertension by Portacaval Shunt. J South Carolina M. A, 46 305–308, 1950.

Potts, W J, Smith, S, and Gibson, S. Anastomosis of the Aorta to a Pulmonary Artery J A M.A, 132.627–631, 1946

Power, W · Contributions to Pathology Maryland Med. & Surg J, 1 306–318, 1840.

Preble, R B Conclusions Based on Sixty Cases of Fatal Gastrointestinal Hemorrhage Due to Cirrhosis of the Liver. Am. J M Sc, 119 263–279, 1900

Prentice, T C, Siri, W, and Joiner, E E · Quantitative Studies of Ascitic Fluid Circulation with Tritium-Labelled Water Am. J Med, 13 668–673, 1952

Prinzmetal, M, Ornitz, E M, Jr, Simkin, B, and Bergman, H. C Arterio-

Roger, G E G Normal and Pathologic Physiology of the Liver Paris, Masson, 1922
Roger, G H Portal Vein Development, Physiology, Pathology Dict encycl d sc med, Paris, 1888, 2 Ser, Vol 26, pp 720–740
Roger, H On Certain Conditions which Modify the Action of the Liver on Microbes Compt Rend Soc de biol, 50 943–946, 1898
Rogers, C. S, Ferguson, C C, Friedgood, C E, and Vars, N M Influence of Fat in the Diet upon Nitrogen Balance and Liver Regeneration Am J Physiol, 163 347–353, 1950
Rolleston, H D, and Fenton, W J On the Cirrhotic Liver Birmingham M Rev, 40 193–215, 1896
——— and McNee, J W Diseases of the Liver, Gall Bladder and Bile Ducts London, The Macmillan Co, 1929
Romer, A S The Vertebrate Body Philadelphia, W B Saunders Co, 1949
Romieu, C, and Brunschwig, A Bacteriologic Study of the Human Liver Surgery, 30 621–623, 1951
Rommelaere, M The Pathology of the Portal Vein I Splenophlebitis Bull Acad roy de méd de Belgique, 17 587–633, 1903
——— The Pathology of the Abdominal Portal System Part 2 Pylethrombosis Brussels, 1905
Rosenak, B D, Moser, R H, Pickett, R D Allen, R K, and Malinowski T The Use of a Cation Exchange Resin in Treatment of Ascites and Edema in Cirrhosis of the Liver Gastroenterology 22 575–585, 1952
Rosenbaum, D, and Egbert, H L Liver Necrosis and Death Following Hepatic Artery Ligation J A M A 149 1210–1212 1952
Rosenbaum, J B Fergerson, B C Davis R K, and Rossmeisel E C The Influence of Cortisone upon the Diurnal Rhythm of Renal Excretory Function J Clin Investigation, 31 507 1952
Rosenstein, P The Treatment of Cirrhosis of the Liver by Construction of an Eck Fistula Arch f klin Chir, 98 1082–1092 1912
Rous, P, and Larimore, L D Relation of the Portal Blood to Liver Maintenance J Exper Med, 31 609–631 1920
Rousselot, L M The Role of Congestion (Portal Hypertension) in So Called Banti's Syndrome Clinical and Pathologic Study of Thirty One Cases with Late Results Following Splenectomy J A M A 107 1788–1793 1936
——— Congestive Splenomegaly (Banti's Syndrome) Bull N Y Acad Med 15 188–196, 1939
——— Combined (One Stage) Splenectomy and Porta Caval Shunts in Portal Hypertension J A M A, 140 282–288 1949
——— Present Concepts in Surgery of the Spleen S Clin North America 29 369–381 1949
——— The Late Phase of Congestive Splenomegaly (Banti's Syndrome) with Hematemesis but without Cirrhosis of the Liver Surgery, 8 34–42 1950
——— Surgical Therapy for Gastrointestinal Hemorrhage in Portal Hypertension Rev Gastroenterol, 18 575–589, 1951
——— Autogenous Vein Grafts in Splenorenal Anastomosis Surgery, 31 403–410, 1952
——— and Thompson, W P Experimental Production of Congestive Splenomegaly Proc Soc Exper Biol & Med, 40 705–708, 1939
Ruysch F Opera omnia anatomico medico-chirurgica Amsterdam, Janssonio Waesbergios, 1720–33

ment of Portal Hypertension with a Report of Six Cases Preliminary Report Bull Johns Hopkins Hosp, *88*.365–375, 1951.

Remak, R. Investigations on the Embryology of Vertebrates. Berlin, G Reimer, 1850–55

Retzius, A On the Structure of the Liver. Oversigt af Kongl Vet.-Akad Forhandl, Jan 1849 Trans in Arch f. Anat, Physiol u wissensch. Med, Berlin, 1849, pp 154–170. Also Trans, Edinburgh M & Surg J., 74 341–352, 1850

Reynell, P C The Prognosis of Portal Hypertension. Lancet, *2*:383–385, 1953

——— Portal Hypertension in the Rat Brit J. Exper Path, *33*.19–24, 1952.

Reynolds, J T, and Southwick, H W.. Portal Hypertension. Use of Venous Grafts when Side-to Side Anastomosis is Impossible. Arch. Surg, *62* 789–804, 1951

Mammalian Liver Morph

...osis with Ascites Ann Int Med, *34* 37–57, 1951

——— Pathological Liver with Minimal or No Change in "Liver Tests" Am J M Sc, *221* 287–292, 1951.

———, Eichelberger, L, and Kirsner, J B · Observations on the Alterations in Electrolytes and Fluid Balance in Patients With and Without Cirrhosis of the Liver J Clin Investigation, *30*·1157–1170, 1951

——— and Kirsner, J B "Latent" Portal Cirrhosis. Gastroenterology, *17*· 184–191, 1951

——— and Wissler, R W Cholangiolitic Biliary Cirrhosis (Primary Biliary

Rindfle[illegible] V. C Klo- Vol 2.

Ripstein, C B, and Lipton, S Varicosity of the Cystic Vein A Hazard of Gallbladder Surgery Ann Surg, *135* 284–286, 1952

Risel, W Contribution on Thrombotic Obliteration and Cavernous Changes of the Portal Vein Deutsch med Wchnschr., *35* 1685–1690, 1909

Ritter, A Results of the Ligature of the Hepatic Artery Contribution on Testing Liver Function Mitt a d Grenzg d. Med u Chir, *35* 76–101, 1922

Robinson, F H, Jr, and Farr, L. E The Relations Between Clinical Edema and the Excretion of an Antidiuretic Substance in the Urine Ann Int Med, *14* 42–54, 1940

Robinson, W L The Vascular Mechanism of the Spleen. Am J Path, *2* 341–354, 1926

——— The Venous Drainage of the Cat's Spleen Am. J Path, *6* 19–25, 1930

Rossle, R The Changes of the Blood Capillaries of the Liver and Their Significance in the Histogenesis of Cirrhosis of the Liver Virchows Arch f path Anat, *188* 484–526, 1907

——— Inflammation of the Liver In Henke and Lubarch Handbuch der speciellen pathologischen Anatomie und Histologie Berlin, Springer, 1930, Vol 5, pt 1, pp 243–505.

———: The Behavior of the Organs in a Patient with Cirrhosis of the Liver. Compt Rend de la première conf. internat de la path géograph, Geneva, Oct 8–10, 1931 Geneva, Kundig, pp. 121–142.

Schutz, W.: Experimental Investigation on the Blood Content of the Liver of the Cadaver with Special Reference to the Congested Liver. Virchows Arch. f. path. Anat., 257:342–365, 1925.

Segall, H. H.: An Experimental Anatomical Investigation of the Blood and Bile Channels of the Liver. Surg., Gynec. & Obst., 37:152–177, 1923.

Senevirathe, R. D.: Physiological and Pathological Responses in the Blood Vessels of the Liver. Quart. J. Exper. Physiol., 35:77–110, 1949.

Sengstaken, R. W., and Blakemore, A. H.: Balloon Tamponage for the Control of Hemorrhage from Esophageal Varices. Ann. Surg., 131:781–789, 1950.

Serege, H.: Contribution to the Study of Portal Circulation in the Liver and its Localization in the Hepatic Lobule. J. de med. de Bordeaux, 31:271–291, 312, 1901.

Shaw, R. E.: Cavernous Sinus Thrombophlebitis. A Review. Brit. J. Surg., 40:40–45, 1952.

Sherlock, S., Bearn, A. G., and Billing, B.: The Effect of Insulin on the Liver in Normal and Diabetic Man. In: Liver Injury. Trans. Tenth Conf. May 21–22, 1951. Josiah Macy, Jr. Foundation, 1951, pp. 205–255.

——— and Walshe, V.: The Use of a Portal Anastomotic Vein for Absorption Studies in Man. Clin. Sc., 6:113–120, 1945.

Shingleton, W. W., Anlyan, W. G., Neill, K. C., and Vance, J. D.: Observation of Changes in Coagulability of Blood in Patients with Pancreatic Disease. Surgical Forum, Am. College of Surgeons, 1952. Philadelphia, W. B. Saunders Co., 1953.

Shorr, E.: Hepatorenal Vasotropic Factors in Experimental Cirrhosis. In: Liver Injury. Trans. Sixth Conf. May 1–2, 1947. Josiah Macy, Jr. Foundation, pp. 33–39.

——— Recent Findings Concerning the Role of the Liver and Kidney in Circulatory Homeostasis. In: Liver Injury. Trans. Eighth Conf. April 28–29, 1949. Josiah Macy, Jr. Foundation, 1950, pp. 60–85.

——— Baez, S., Zweifach, B. W., Payne, M. A., Mazur, A., and Metz, D. B.: The Antidiuretic Action of the Hepatic Vasodepressor Ferritin (V.D.M.) and its Occurrence in Condi[illegible] Associated with Antidiuresis in Man. Tr. A. [illegible] 49, 1950.

———, Zweifach, [illegible] Occurrence, Sites and [illegible] Affecting Compensa[illegible] [illegible] Shock. Science, 102:489–

Shrock, [illegible] Janzen, J., and Barnard, M. C.: Report of a New Born Human Presenting Sympus Dipus. Anomalous Umbilical Vein, Transposition of the Viscera and Other Anomalies. Anat. Rec., 82:347–360, 1942.

Simonds, J. P.: A Study of the Simultaneous Changes in Blood Pressure in the Carotid Artery and Jugular and Portal Veins in Anaphylactic and Peptone Shock in the Dog. Am. J. Physiol., 65:512–526, 1923.

——— *Pathological Physiology of the Liver.* Quart. Bull., Northwestern Univ. M. School, 14:242–249, 1940.

——— and Brandes, W. W.: The Effect of Obstruction of the Hepatic Veins on the Systemic Circulation. Am. J. Physiol., 72:320–323, 1925.

Sims, J. L.: A Comparison of Renal Function with Urinary Antidiuretic Activity in Cirrhosis of the Liver with Ascites. J. Lab. & Clin. Med., 36:990, 1950.

Sabatier, R. B. Complete Treatise on Anatomy. Paris, Barrois, 1781.
Sabin, F. R., Doan, C. A., and Cunningham, R. S.: Discrimination of Two Types of Phagocytic Cells in the Connective Tissues by the Supravital Technique. Contrib. Embryol. No. 52, Carnegie Institution, Washington, 16:125–218, 1925.
Sabourin, C. Contribution to the Study of the Parenchyma of the Liver in
——— [illegible] atic Veins: Their Role in the [illegible] méd., Paris, 4:617–627, 1884
——— Cirrhosis of the Liver of Cardiac Origin. Rev. de méd., Paris, 6:29–49, [illegible]
——— and Mallon, P. Digestive Hemorrhages Treated by Splenectomy and Spleno-Renal Anastomosis. Arch. d. mal. de l'app. digestif, 40:929–932, 1951.
Sappey, P. C. Research on Certain Accessory Portal Veins. Mém. Soc. Biol., 11:3–13, 1859.
——— [illegible]
Saunders [illegible]
Blood-Letting Letter of 1535, with Annotated Translation and Study of the Evaluation of Vesalius' Development. New York, H. Schuman, 1948
Schafer, P. W., and Kittle, C. F. Partial Esophagogastrectomy in the Treatment of Esophagogastric Varices. Arch. Surg., 61:235–242, 1950.
Schiff, M. A New Function of the Liver. M. Times & Gaz., 1:621–622, 1877
——— Ligature of the Portal Vein. Rev. méd. de la Suisse Rom., Geneva, 1:38–43, 1881.
Schilling, J. A., McKee, F. W., and Wilt, W. Experimental Hepatic-Portal [illegible]
Schloer [illegible]
——— [illegible]
Deuterium Oxide Dilution. J. Clin. Investigation, 29:1296–1309, 1950
[illegible]
of the Permeability Factor in Ascites and Edema Using Albumin Tagged with I^{131}. Gastroenterology, 22:607–619, 1952.

tion of the Portal Vein Virchows Arch f path Anat, 62 195–200 1875

ew Approach to the Treatment of 35 628–629 1947

nd Mann F C The Mechanism of the Liver Am J Physiol, 124 555–566, 1938

Southw ular Grafts in Portacaval ollege of Surgeons, 1950 195–200

Spaltch h Ed Philadelphia J B

Anat Anz

3rd Ed Chicago, S B Debour, 1941

Stahl, G E De venae portae In Haller Disputationes anatomicae, 3 131 1748

——— De venae portae, porta malorum hypochondriaco splenico suffocativo-hysterico-colico haemorrhoidariorum (Recusa) Haloe ad Salam sumpt, J C Hendelin, 1751

Starling, E H The Influence of Mechanical Factors on Lymph Production J Physiol, 16 224–267, 1894

Steenhuis Experimenteel en kritisch onderzoek de gevolgen dar poortader aastuitung Inaug Diss, Groningen 1911

Steinberg B, and Martin R A Absorption of Scar Tissue in Experimental Nodular Cirrhosis of the Liver With a Method of Visualizing Cirrhotic Changes Arch Path 41 1–10 1946

Stephanson G W Experimental Pathology of the Liver Arch Path 14

Man as Measured by 1128–1236 1951

n as Measured by Du 235–1242 1951

——— W J The Serum Pro igement J Clin Investi

onic Cirrhosis Its Clinical –179 1952

Produced Cyclopean Fish—"The Magnesium Embryo" J Exper Zool 6 255–336 1909

——— Developmental Rate and Structural Expression Am J Anat, 28 116–262, 1921

Stohr In Elias, 1949

Stolnikow The Place of the Hepatic Veins in the Liver and General Circulation Pflugers Arch f ges Physiol 28 255–286 1882

Strauss M B, Davis R K Rosenbaum J D and Rossmeisel, E C Production of Increased Renal Sodium Excretion by the Hypotonic Expansion of Extracellular Fluid Volume in Recumbent Subjects J Clin Investigation 31 80–85 1952

Strickler J H Enfkin N and Rice C O Hepatic Portal Arteriovenous Fistula Surgery 31 583–588 1952

Sims, J L, Morris, L E, Orth, O S, and Waters, R M. The Influence of Oxygen and Carbon Dioxide Levels During Anesthesia upon Post Surgical Hepatic Damage J Lab Clin Med, *38* 388–395 1951
Singh, B, and Sohal H S Variations of the Hepatic Artery and Its Branches Indian J Surg, *14* 20–32, 1952
Sirota, J H, Baldwin, D S, and Villarreal, H. Diurnal Variations of Renal Function in Man J Clin Investigation, 29 187–192, 1950
Slavjansky, K The Dependence of the Central Circulation of the Blood on the Sensitivity of the Sympathetic Nerves of the Vessels. Arb Physiol Anst, Leipzig, 8 251–280, 1873
Smalley, R E, Binger M W, Bollman, J L, and Power, M. H Effect of Intravenously Administered Solution of Acacia on Animals. Arch. Int Med, *76* 39–46, 1945
Smith, H P, Belt, A E, and Whipple, G H Rapid Blood Plasma Protein Depletion and the Curve of Regeneration Am. J Physiol, 52.54–71, 1920
Smith, R M, and Farber S Splenomegaly in Children with Early Hematemesis J Pediat, *7* 585–608, 1935
Snell, A M Clinical Aspects of Portal Cirrhosis Ann Int. Med, *5* 338–355, 1931
——— Changing Conceptions of Portal Cirrhosis Pennsylvania M. J, *45*: 337–344, 1942
——— Some Clinical and Physiological Problems in Cases of Portal Cirrhosis North Carolina M J, *8* 338–346, 1947
——— Discussion of Symposium on Hepatic Circulation Proc Staff Meet, Mayo Clin, *25* 36–38, 1950
———, Green, C H, and Rowntree, L G Diseases of the Liver. VII Further Studies in Experimental Obstructive Jaundice Arch Int Med, *40* 471–487, 1927
Snook, T A Comparative Study of the Vascular Arrangements in Mammalian Spleens Am. J Anat, *87* 31–59, 1950.
Snyder, C D Experimental Studies on Vagal Control of the Functions of the Liver Am J Physiol, *118* 345–353, 1937.
——— Vascular Events and Volume Changes in the Turtle's Liver Surviving in an Oncometer Am J Physiol, *124* 647–661, 1938
——— Recent Advances in Knowledge of the Liver Physiol. Rev, 22 54–70 *1942*
——— Some Vascular Responses within the Liver and their Interpretation *Rev Gastroenterol, 9 230–235, 1942*
——— and Martin, L E Vascular Reaction to Epinephrin in Perfusates of Various C_H II. The Portal-Venous System of the Liver Am. J Physiol, *62* 185–191, 1922
——— and Tyler, F H Oxygen and Carbon Dioxide Exchanges in the Turtle's Liver. J Cell & Comp Physiol, *16* 135–146, 1940
——— and Tyler, F H Metabolism Studies on Surviving Turtle's Liver. J Cell & Comp Physiol, *16* 377–388, 1940
5th Ed New York, Stechert, 1939

Zentrlbl f Chir, *11* 664, 1884

tion of the Portal Vein Virchows Arch f path Anat, 62 195–200 1875

Sohn, M L., and Carlock, J. H A New Approach to the Treatment of Esophageal Varices J A M A 135 628–629 1947

Soskin S, Essex, H E, Herrick, J F, and Mann F C The Mechanism of Regulation of the Blood Sugar by the Liver Am J Physiol, 124 558–566, 1938

Southwick, H. W The Experimental Use of Vascular Grafts in Portacaval Anastomosis Surgical Forum, American College of Surgeons 1950 Philadelphia, W B Saunders Co 1951 pp 195–200

Spalteholz, W Hand Atlas of Human Anatomy 7th Ed Philadelphia J B Lippincott Co, 1937

Spanner, R. The Arterio-Venous Anastomoses in the Intestine Anat Anz Suppl, 1931, pp 24–26

Spivack, J L The Surgical Technic of Abdominal Operations 3rd Ed Chicago S B Debour 1941

Stahl G E De venae portae In Haller Disputationes anatomicae 3 131, 1748

——— De venae portae, porta malorum hypochondriaco splenico-suffocativo hysterico-colico haemorrhoidariorum (Recusa Halae ad Salam sumpt, J C Hendelu, 1751

Starling E H The Influence of Mechanical Factors on Lymph Production J Physiol, 16 224–267 1894

Steenhuis Experimenteel en kritisch onderzoeck de gevolgen dar poortader aistuiting Inaug Diss Groningen 1911

Steinberg, B, and Martin R A Absorption of Scar Tissue in Experimental Nodular Cirrhosis of the Liver With a Method of Visualizing Cirrhotic Changes Arch Path 41 1–10 1946

Stephanson, G W Experimental Pathology of the Liver Arch Path 14 484–490 1932

Sterling K The Turnover Rate of Serum Albumin in Man as Measured by I131 Tagged Albumin J Clin Investigation 30 1128–1236 1951

——— The Turnover Rate of Serum Albumin in Man as Measured by I131 Tagged Albumin J Clin Investigation 30 1238–1242 1951

———, Ricketts, W E Kirsner J B and Palmer W L The Serum Proteins in Portal Cirrhosis under Medical Management J Clin Investigation 28 1236–1245 1949

Stine, L A, and Swarts J M Post Necrotic (Toxic) Cirrhosis Its Clinical Significance Am J Digest Dis 19 176–179 1952

Stockard C R The Development of Artificially Produced Cyclopean Fish—"The Magnesium Embryo" J Exper Zool, 6 285–336 1909

——— Developmental Rate and Structural Expression Am J Anat 28 116–262, 1921

Stohr In Ellis, 1949

Stolnikow The Place of the Hepatic Veins in the Liver and General Circulation Pflugers Arch f ges Physiol 28 255–256 1882

Strauss, M B, Davis R K Rosenbaum J D and Rossmeisel E C Production of Increased Renal Sodium Excretion by the Hypotonic Expansion of Extracellular Fluid Volume in Recumbent Subjects J Clin Investigation 31 80–85 1952

Strickler J H Lufkin, N, and Rice C O Hepatic Portal Arteriovenous Fistula Surgery, 31 583–588, 1952

Sims, J. L., Morris, L. E., Orth, O. S., and Waters, R. M.: The Influence of Oxygen and Carbon Dioxide Levels During Anesthesia upon Post Surgical Hepatic Damage. J. Lab. Clin. Med., 38:388–395, 1951.
Singh, B., and Sohal, H. S.: Variations of the Hepatic Artery and Its Branches. Indian J. Surg., 14:20–32, 1952.
Sirota, J. H., Baldwin, D. S., and Villarreal, H.: Diurnal Variations of Renal Function in Man. J. Clin. Investigation, 29:187–192, 1950.
Slavjansky, K.: The Dependence of the Central Circulation of the Blood on the Sensitivity of the Sympathetic Nerves of the Vessels. Arb. Physiol. Anst., Leipzig, 8:251–280, 1873.
Smalley, R. E., Binger, M. W., Bollman, J. L., and Power, M. H.: Effect of Intravenously Administered Solution of Acacia on Animals. Arch. Int. Med., 76:39–46, 1945.
Smith, H. P., Belt, A. E., and Whipple, G. H.: Rapid Blood Plasma Protein Depletion and the Curve of Regeneration. Am. J. Physiol., 52:54–71, 1920.
Smith, R. M., and Farber, S.: Splenomegaly in Children with Early Hematemesis. J. Pediat., 7:585–608, 1935.
Snell, A. M.: Clinical Aspects of Portal Cirrhosis. Ann. Int. Med., 5:338–355, 1931.
——— Changing Conceptions of Portal Cirrhosis. Pennsylvania M. J., 45:337–344, 1942.
——— Some Clinical and Physiological Problems in Cases of Portal Cirrhosis. North Carolina M. J., 8:338–346, 1947.
——— Discussion of Symposium on Hepatic Circulation. Proc. Staff Meet., Mayo Clin., 25:36–38, 1950.
———, Green, C. H., and Rowntree, L. G.: Diseases of the Liver. VII. Further Studies in Experimental Obstructive Jaundice. Arch. Int. Med., 40:471–487, 1927.
Snook, T.: A Comparative Study of the Vascular Arrangements in Mammalian Spleens. Am. J. Anat., 87:31–59, 1950.
Snyder, C. D.: Experimental Studies on Vagal Control of the Functions of the Liver. Am. J. Physiol., 118:345–353, 1937.
——— Vascular Events and Volume Changes in the Turtle's Liver Surviving in an Oncometer. Am. J. Physiol., 124:647–661, 1938.
——— Recent Advances in Knowledge of the Liver. Physiol. Rev., 22:54–70, 1942.
——— Some Vascular Responses within the Liver and their Interpretation. Rev. Gastroenterol., 9:230–235, 1942.
——— and Martin, L. E.: Vascular Reaction to Epinephrin in Perfusates of Various C[illegible] II. The Portal-Venous System of the Liver. Am. J. Physiol., 62:185–191, 1922.
——— and Tyler, F. H.: Oxygen and Carbon Dioxide Exchanges in the Turtle's Liver. J. Cell. & Comp. Physiol., 16:135–146, 1940.
——— and Tyler, F. H.: Metab[illegible] s on Surviving Turtle's Liver. J. Cell. & C[illegible] 940
New York, Stechert, 1939.
[illegible] J. Clin., 11:664, 1884.
[illegible] Complications in Polythemia Vera. Arch. Int. Med., 62:925–943, 1938.
Solowieff, A.: Changes in the Liver under the Influence of Artificial Obstruc

Thompson, R B Thrombosis of the Hepatic Veins The Budd Chiari Syndrome Arch Int Med, 80,602–613, 1947
Thompson, W. P The Pathogenesis of Banti's Disease, Ann Int Med, 14 255–261, 1940
——, Caughy, J L, Whipple, A O and Rousselot, L. M Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome) J Clin Investigation, 16 571–572, 1937
Thoms

——
Liver J Anat & Physiol, 33 546–564, 1899
Thomson, W A Practical Treatise on the Diseases of the Liver and Biliary Passages Edinburgh, 1841, Philadelphia, 1842
Thomson, W H Contribution to the Physiological Effects of Peptone when

tionation J Clin Investigation, 25 304–322, 1946
Thors, R, Grindlay, J H, and Bollman, J L Effect of Ligation of the Hepatic Artery on Oxygen Content of Blood from the Hepatic Vein in Dogs, Surgical Forum, American College of Surgeons, 1952 Philadelphia, W B Saunders Co, 1953
Tiedemann, F, and Gmelin, L Investigation on the Manner in which Substances from the Stomach and Intestines Reach the Blood Heidelberg, 1820
Tigerstedt, R Textbook of Physiology of the Circulation Leipzig, Veit, 1893
Trew, C J Dissertatio epistolica de differentiis quibusdam inter hominem natum et nascendum intercedentibus deque vestigiis divini numinis inde colligendis Norimbergae prostat apud Petr Conr Monath, 1736
Tuffier, M Intubation in Wounds of the Great Arteries Bull Acad de méd, Paris, 74 455–460, 1915
—— Wounds of the Arteries Bull et mém Soc de Chirurgiens de Paris, 43 1469–1471, 1917
Tuffier
Tvor, A

in the Urine of Patients with Cirrhosis Gastroenterology, 21 79–88 1952
——
nan
ion,
s in
Umbrei
ein
390, 1947

Ed by W D Andrus New York, Interscience Publishers, 1950, Vol 2, pp. 41–78
Symmers, W St C Portal Embolism Following Thrombosis of Splenic Vein and Causing Infarct-Like Cyanotic Atrophy (Zahn's Infarct) of the Liver Brit J Surg, 38 498–502, 1951.
Talma, S Benign Parenchymal Hepatitis Berl. klin Wchnschr. 28 1110–1113, 1891
——— Surgical Opening of a New Channel for the Blood of the Vena Porta Berlin klin Wchnschr, 35 833–836, 1898, 41 893–897, 1904.
——— Cirrhosis of the Liver Handl. van het XII Nederlandsch Natuuren Geneeskundig Congres, Utrecht, April 15–17, 1909. Haarlem, Kleynenberg, 1909
Tanner, N C End-in-Side Spleno-Renal Venous Anastomosis Proc. Roy.

Tansini

———

atti d soc ital di Chir., 17 59–65, 1902.
Tantum, C, Swigert, L L, and Campa, J. F.: Prevention of Death from Ex ... Branches of the ... 1950.
Tappen ... r Ligation of the Portal Vein Ber u d verhandl d (K) Sachs Ges d. Wissensch. z Leipzig, Math-Phys Kl, 24 193–246, 1872. Also Arb Physiol Anstalt z Leipzig, 7 11–64, 1872.
Tarail, R Nutrition in Liver Disease. Pennsylvania M. J, 54 1144–1149, 1951
Thiel, G A, and Downey, H The Development of the Mammalian Spleen with Special Reference to Its Hematopoietic Activity. Am J. Anat., 28 279–328, 1921
Thiele In Rud Wagner's Handworterbuch der Physiologie Braunschweig, 1844–1850, Vol 2, 308, 362
Thole, F Injuries of the Liver and Gallbladder In. Neue Deutsche Chirurgie. Ed by P v Bruno Stuttgart, F Enke, 1912, Vol 4.
——— Surgery of Tumors of the Liver In Neue Deutsche Chirurgie Ed by P v Bruno Stuttgart, F Enke, 1913, Vol 7.
Thoma Investigation on the Histogenesis and Histomechanism of the Vascular System. Stuttgart, F Enke, 1893
——— Textbook of General Pathology and Pathological Anatomy Trans by Bruce London, Black, 1896
Thomas Two Cases of Inflammation of the Portal Vein Deutsch Klin, Berlin, 5 302–304, 1853
Thomas, R. Contribution to Differential Diagnosis between Obstruction of the Portal Vein and the Inferior Vena Cava Cassel, Bibliog Med, pt 1, no 2, 1895
Thomas, S F, Henry, G W, and Kaplan, H S Hepatolienography Past, Present and Future Radiology, 57 669–684, 1951.
Thompson, J M. Arteries in the Hepatic Pedicle; Study in Statistical Human Anatomy. Univ California Publ, Anat, 1 55–159, 1933

Thompson, R. B Thrombosis of the Hepatic Veins The Budd-Chiari Syndrome, Arch Int Med, 80 602–613, 1947
Thompson, W P The Pathogenesis of Banti s Disease Ann. Int Med, 14 255–261, 1940
———, Caughy, J L, Whipple, A O and Rousselot, L M Splenic Vein Pressure in Congestive Splenomegaly (Banti s Syndrome) J Clin Investigation, 16 571–572, 1937
Thomson, A Report of the Committee of Collective Investigation of the

Injected into the Circulation J Physiol, 25 1–21, 1899
Thorek, P Ligation of the Common Hepatic Artery in Portal Hypertension [illegible]

1820
Tigerstedt, R Textbook of Physiology of the Circulation Leipzig, Veit, 1893
Trew, C J Dissertatio epistolica de differentiis quibusdam inter hominem natum et nascendum intercedentibus deque vestigiis divini numinis inde colligendis Norimbergae prostat apud Petr Conr Monath, 1736
Tuffier, M Intubation in Wounds of the Great Arteries Bull Acad de méd, Paris, 74 455–460, 1915
——— Wounds of the Arteries Bull et mem Soc de Chirurgiens de Paris, 43 1469–1471, 1917
Tuffier, T Aneurism of the Hepatic Artery Presse méd, 18 153–154, 1909
Tyor, M P, Aikawa J K, and Cayer, D Measurements of the Disappearance of Radioactive Tagged Albumin from Serum and the Excretion of I131 in the Urine of Patients with Cirrhosis Gastroenterology, 21 79–88 1952
——— and Cayer, D The Rate of Disappearance of Iodinated Human Albumin from the Serum in Relation to Albumin Concentration, Total Circulating Albumin Content, and the Presence of Ascites in Patients with Cirrhosis J Lab & Clin. Med, 39 874–880, 1952
Umbreit A Case of Thrombosis of the (Leberveinen) and the Portal Vein Virchows Arch f d ges Physiol, 183 102–113, 1906
Urlings, G Portacaval Shunt in Esophageal Hemorrhage Belg d tijdschr geneesk, 6 773–790, 1950
Vars, H M, and Gurd, F. N Role of Dietary Protein in Experimental Liver Regeneration A Nitrogen Balance Study Am J Physiol, 151 391–398, 1947

Vars, H M, and Gurd, F. N Effect of Dietary Protein upon the Regeneration of Liver Protein in the Rat. Am. J. Physiol, *151*:399–403, 1947.
Verney, E B *The Antidiuretic Hormone and the Factors which Determine its Release* Proc Roy Soc London, Ser. B, *135*:25–104, 1947
——— Agents Determining and Influencing the Functions of the Pars Nervosa of the Pituitary Brit M J, 2 119–123, 1948
Verse, M On Cavernous Changes of the Tissues around the Portal Vein in Old Portal Thrombosis. Beitr z path Anat u z allg Path, *48* 526–537, 1910
Vesalius, A De humani corporis fabrica. Basileae, ex off. J. Oporini, 1543.
——— Radicis chymae usus Lugduni, Io. Frellonius, 1547.
——— De radice chyme In Luisinus, Aloysius De Morbo Gallico Venetus, 1566–1567, Vol. I, pp. 504–514
Vidal, E Surgical Treatment of Ascites. Presse méd., *11*:747, 1903
——— Discussion of the Eck Operation Rev. Chir., Paris, *42*:1181–1182, 1910
Villard, E, and Tavernier, L Ovario Mesenteric Suture in a Case of Cirrhosis of the
Villaret, M.
sion
Steinheil, 1906
Volweiler, W, Grindlay, J. H and Bollman, J L The Relation of Portal Pressure to the Formation of Ascites An Experimental Study. Gastroenterology, *14* 40–55, 1950
———, Bollman, J L, and Grindlay, J H. A Comparison of Two Types of Experimental Ascites Proc Staff Meet, Mayo Clin, 25.31–33, 1951
Von Basch The Influence of the Stimulated Splanchnic Nerve on the Blood Stream within and without its Region Arb a d physiol. Anst, Leipzig, *10* 229–277, 1875
Von Bielka Demonstration and Communication on the Anastomoses of the Inferior Vena Cava with the Portal Vein Wien klin. Wchnschr, *12* 205–207, 1899
Von Haller, A. *Disputationum anatomicarum selectarum*, Gottingen, Abram Vandenhoeck, 1746–51
——— Elementa physiologiae corporis humani Lausanne, 1757–63, Berne, 1764–66
——— Opera minora Lausanne, F Grasset, 1763–68.
Von Kupffer, C On the So-Called Stellate Cells of the Mammalian Liver
Von M
Wagenl
Waite,
Wakim
307–311 1942
———
———

Circulation of Blood in the Intact Animal. Arch Path, 33 198–203, 1942
——— and Mann, F C The Intrahepatic Circulation of Blood Anat Rec, 82 233–251, 1942
Walcker, F Contribution to Knowledge of Collaterals the Circulation of the Blood in the Portal System Langenbeck's Arch f klin Chir, 120 819–858, 1922
Waleus De motu chyli et sanguinis, ad T Bartholinum, epistola seconda, 1640
Walker, R M The Pathology and Treatment of Portal Hypertension Lancet, 1,729–733, 1952
Wallgren, A Contribution to the Study of Splenomegaly in Infancy Acta paediat, Suppl, 6 1–120, 1927
Walters, W, Moersch, H J and McKinnon, D A Bleeding Esophageal Varices An Evaluation of Methods Directed Toward their Control, Especially by Injection of a Sclerosing Solution Arch Surg, 41 1101–1117 1940
——— Rowntree, L G, and McIndoe A H Ligation of the Coronary Veins for Bleeding Esophageal Varices Proc Staff Meet, Mayo Clin, 4 146–147, 1929
Wangensteen, O H Discussion of Phemister and Humphreys
——— Surgical Lesions of the Esophagus Including Discussions of Esophagitis 'Spontaneous (Acid Peptic) Perforation of the Esophagus, Dystonia (Cardiospasm) Para-esophageal Hernia, Varices and Can
[illegible]

———

Warthi[illegible]

225, 1910
Wasserman, K and Mayerson, H S Exchange of Albumin between Plasma and Lymph Am J Physiol, 165 15–26, 1951
Watson, C J, and Greenberg, A Certain Effects of Salt Poor Human Albumin in Cases of Hepatic Disease Am J M Sc, 217 651–656, 1949
Weatherford, H L The Influence of Anaphylactic Shock on the Finer Structure of the Liver in the Dog Am J Path 11,611–626, 1935
Webber, R J, and Coe, J I Rupture of Pyogenic Hepatic Abscess into the Hepatic Vein Surgery, 27 907–910 1950
Weber, E H Annatationes anatomica et physiologicae Programmata collecta Ber u d Verhandl d (K) Sachs Ges z Leipzig, 1850, pp 185
Weber, F P Acute Degeneration of Liver Cells Supervening in the Course

———

———

Weinb[illegible]

inversus Bull Internat Ass Med Mus, 30 63–74, 1949
Welch, C S, and Callow, A D. Appraisal of Current Methods for Treatment of Portal Hypertension Rev Gastroenterol, 17,423–438, 1950.

Operation for Ascites New

Case in which the Operation
, 1866.
bdominal Tumors. Philadel-
urchill, 1885.

——— Remarks on Splenectomy with a Report of a Successful Case. Brit M J, 1 796, 1888

Wepfer, J J De dubiis anatomicis epistola ad J H. Paulm Nuremberg, 1644.

Wertheimer, F Development of the Liver and Portal System. Lille, 1883

——— Investigations on the Umbilical Vein. J. de l' anat. et physiol., 22. 1–16, 1886

——— Investigation on the Intact Circulation of Various Organs in the Frog Pfluger's Arch f d ges. Physiol, *196*·412–422, 1922.

West, G B Injections of Adrenalin and Noradrenalin, and Further Studies on Liver Sympathin Brit J Pharmacol, *3*·189–197, 1948.

Wharton, G K Blood Supply of Pancreas, with Special Reference to That of the Islands of Langerhans Anat Rec, *53*.55–74, 1932.

Whelan, T J, McCoord, A B, and Schilling, J. A · Experimental Ascites The Influence of Transplantation of the Kidneys to the Neck. Surgical Forum, American College of Surgeons, 1952. Philadelphia, W. B Saunders Co, 1953

Whipple, A O Studies in Splenopathy Introduction. J A M.A, *107*.1775–1776, 1936

——— The Combined Spleen Clinic Results with Medical and Surgical Treatment of the Splenopathies Surg, Gynec. & Obst., *64* 296–302, 1937

——— Surgical Treatment of Carcinoma of the Ampullary Region of the Head of the Pancreas Am J Surg, *40*·260–263, 1938

——— The Medical Surgical Splenopathies. Bull. New York Acad Med, *15* 174–176, 1939

——— Recent Studies in the Circulation of the Portal Bed and of the Spleen in Relation to Splenomegaly Tr & Stud., Coll Physicians, Philadelphia, *8* 203–212, 1941

——— The Problem of Portal Hypertension in Relation to Hepatosplenopathies Ann Surg, *122* 449–473, 1945

——— The Rationale of Porta Caval Anastomosis. Bull. New York Acad Med., *22* 251–253, 1946

——— Portal Bed Block and Portal Hypertension. In. Advances in Surgery. Ed by W D Andrus New York, Interscience Publishers, 1949, Vol 2, pp 155–178

Whipple, G H, and Robscheit-Robbins, F S. Control Basal Diets in Anemic Dogs Methods, Factors and Hemoglobin Production. Am J. Physiol, *115* 651–661, 1936

———, Robscheit-Robbins, F S, and Hawkins, W B Eck Fistula Liver Subnormal in Producing Hemoglobin and Plasma Proteins on Diets Rich in Liver and Iron J. Exper Med, *81* 171–190, 1945

———, Smith, H. P and Belt, A E H Shock as a Manifestation of Tissue Injury Following Rapid Plasma Protein Depletion. Am J Physiol, *52*·72–100, 1920.

——— and Sperry, J A Chloroform Poisoning, Liver Necrosis and Repair. Bull. Johns Hopkins Hosp, *20*.278–289, 1909.

Clin Investiga

White,

Pr... 40 I..47 1897

2nd

—— ... -116,
1947

—— Am

J

—— under
Experimental Conditions, Including Hemorrhagic Shock Am J Physiol, 146 192-206, 1946

Wiles, C F, Jr, Schenk, W G, Jr, and Lindenberg, J The Experimental Production of Portal Hypertension Ann Surg, 136 811-817, 1952

—— Schenk, W G, Jr, and Lindenberg, J Influence of Hepatic Artery Ligation on Regeneration of Liver Tissue in the Rat Arch Surg, 64 783-787 1952

Wilkin

Wilson,
Inflammation Trans Soc Improv Med & Chir Knowledge, London, 3 65, 1804-12

Wilson, J W

Winternitz M Vessels
upon th 11

Wohlwill F nchous
Arch f path Anat, 254 243-270, 1925

Wolbach, S B, and Saiki, T A New Anaerobic Spore-Bearing Bacterium Commonly Present in the Liver of Healthy Dogs, and Believed to be Responsible for Many Changes Attributed to Aseptic Autolysis of Liver Tissue J Med Research, 21 267-278, 1909

Womach, N A The Surgery of Portal Hypertension In Operative Technique Ed by W H Cole New York, Appleton Century-Crofts Co,

of the Pancreas Anat Rec,

J F Infarcts of the Liver
Gastroenterology, 17 479-492, 1951

Yater W M Histopathologic Study of Tissues of Sixty Five Patients Injected with Thorium Dioxide Sol for Hepatosplenography, Am J M Sc, 195 198-205, 1938

—— and Coe, F O Ten Years' Experience with Thorotrast Hepatosplenography Ann Int Med, 18 350-365, 1943

Welch, K J Failure of the Peritoneal Button Operation for Ascites. New England J Med, *237*:735–737, 1947.
Wells, S Excision of Enlarged Spleen, with a Case in which the Operation was Performed. M Times & Gaz, *1*,2–5, 1866
——— Diagnosis and Surgical Treatment of Abdominal Tumors. Philadelphia, Blakiston, 1885, London, J. & A. Churchill, 1885.
——— Remarks on Splenectomy with a Report of a Successful Case. Brit M J, *1* 796, 1888.
Wepfer, J J De dubis anatomicis epistola ad J. H. Paulin Nuremberg, 1644.
Wertheimer, E Development of the Liver and Portal System Lille, 1883
——— Investigations on the Umbilical Vein. J de l' anat et physiol, 22 1–16, 1886.
——— Investigation on the Intact Circulation of Various Organs in the Frog Pfluger's Arch f d ges Physiol., *196* 412–422, 1922.
West, G. B Injections of Adrenalin and Noradrenalin, and Further Studies on Liver Sympathin Brit J Pharmacol, *3*.169–197, 1948
Wharton, G K Blood Supply of Pancreas, with Special Reference to That of the Islands of Langerhans Anat Rec, *53*:55–74, 1932.
Whelan, T J, McCoord, A B, and Schilling, J. A Experimental Ascites The Influence of Transplantation of the Kidneys to the Neck. Surgical Forum, American College of Surgeons, 1952 Philadelphia, W. B Saunders Co, 1953
Whipple, A O Studies in Splenopathy Introduction. J A M A, *107*.1775–1776, 1936
——— The Combined Spleen Clinic Results with Medical and Surgical Treatment of the Splenopathies Surg, Gynec. & Obst, *64*.296–302, 1937
——— Surgical Treatment of Carcinoma of the Ampullary Region of the Head of the Pancreas Am J Surg, *40* 260–263, 1938.
——— The Medical-Surgical Splenopathies Bull. New York Acad. Med,

———

phia, 8 203–212, 1941
——— The Problem of Portal Hypertension in Relation to Hepatosplenopathies Ann Surg, *122* 449–473, 1945.
——— The Rationale of Porta Caval Anastomosis. Bull. New York Acad

———

2, pp 155–178
Whipple, G. H, and Robscheit-Robbins, F S Control Basal Diets in Anemic Dogs Methods, Factors and Hemoglobin Production Am J. Physiol, *115* 651–661, 1936
——— Eck Fistula Liver Proteins on Diets , 1945
———, Smith, H. P. and Belt, A. E. II Shock as a Manifestation of Tissue Injury Following Rapid Plasma Protein Depletion Am J Physiol, 52.72–100, 1920
——— and Sperry, J A Chloroform Poisoning, Liver Necrosis and Repair. Bull. Johns Hopkins Hosp, *20* 278–289, 1909

INDEX

NOTE Names of authors cited are *italicized* Page numbers in *italics* refer to illustrations

——— and White, C. S. Roentgenographic Demonstration of an Arteriovenous Aneurism by Means of Thorotrast. Am. J. M.Sc., 186:493–495, 1933.

Young, M. O. Common Trunk of Pulmonary Veins Tributary to the Portal Vein, with Multiple Cardiac Anomaly. Arch. Path., 44:169–175, 1947.

Zamcheck, N., Chalmers, T. C., White, F. W., and Davidson, C. S.: Bromsulphalein Test in Early Diagnosis of Liver Disease in Gross Upper Gastrointestinal Hemorrhage. Gastroenterology, 14:343–363, 1950.

Ziegenspeck, R. Study of the Double Junction of the Inferior Vena Cava in the Vestibule of the Heart. Samml. klin. Vortrage, Gynak., 148:405–430, 1905.

——— Fetal Circulation. Gynaek. Rundschau, 4:585–599, 1910.

INDEX

NOTE Names of authors cited are *italicized* Page numbers in *italics* refer to illustrations